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MEDICINE AND THE DOCTOR IN WORD AND EPIGRAM*

SARA M. JORDAN, M.D.†

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THE honor that you have conferred upon me by electing me to this office carries with it an obligation that my predecessors have discharged with such a diversity of subjects as to allow free rein to my imagination. It seemed to me, therefore, a unique opportunity to revert to a premedical (now almost a prehistoric) interest of mine, philology, a love of words, and in its light, to scan the field of medicine. It was quite obvious from words and facial expression of the friends to whom I confided my plan that they thought very little of it, such questions as "Can you make it cohesive?" and "Is such a subject of any interest to busy doctors?" indicating their doubts. There is an ancient maxim "Many receive advice, few profit by it," and am one of the millions who make that maxim a truth.

I do not propose a profound and scientific discussion of what is to me a fascinating study but will be content if some of the entertainment and enjoyment I have had in my preparation sifts through and in some slight degree captivates my captive audience. If your oratrix succeeds in this purpose you will hear a sketch in the Webster definition of the word "a literary composition, short, intentionally slight in treatment, discursive in style and familiar in tone."

My subject is not alien to the doctor. Words are the tools of our art and of the allied sciences. We use words often long, elaborately constructed and hard to spell to name parts, structures, functions and deviations of the human body as a part of our scientific equipment. Shorter words as a method of communicating to our patient the state of his health and its needs are a part of the art of healing. In some branches of our profession they are actually materia medica, words used "as the physicians of a distempered mind" as Aeschylus had it. In medicine as in statecraft and propaganda, words are sometimes the most powerful drug we can use, a thought I cheerfully borrow from Kipling. Parenthetically at this point I should warn you that this sketch, like *Hamlet*, is full of quotations.

The English language is the product of the activities of our English ancestors — Anglo-Saxon, a blend of West German and Scandinavian combined because of the Norman invasion with Norman-French and classical influences. Shorn of these later influences the Anglo-Saxon vocabulary with its simplicity would have been much larger than its present residuum actually is and would have given us a more direct and obvious lineage. For example, a book written in 1340 that we would call by words of classical origin, "The Remorse of Conscience," was named "The Againbite of Inwit" (The Ayenbite of Ynwit).

The phrase agenbite of inwit was adopted by James Joyce in *Ulysses* to describe the anguish of the vulture hours when conscience makes cowards of men. It could not be better as a phrase, and the language made itself poorer when it substituted for agenbite its exact but pallid equivalent the word remorse, which derives from *re*, again, and *mordere*, to bite and the Latin *conscience* for the incisive *inwit* of the Saxon.

A language grows with the activities of those who use it; centuries of changes produce variations and developments in words and structure that characterize those changes. Although Anglo-Saxon words have to some extent fallen into disrepute because so many of them are spelled with four letters, regret may with propriety be felt for the loss of some of them. We made a bad trade when we exchanged the forthrightness and the rightness of certain Saxon monosyllabics for the polite and painfully constructed polysyllabics of the medical pundits. Our language thereby lost some of its essential guts. However, we still know many of the outward parts of the body and the chief internal structures by Anglo-Saxon words: arm, hand, finger, nose, eye, ear, skin, heart, brain, lung, kidney, liver and bone, but most of the adjectives describing these parts of the body succumbed to the Normans — ocular, aural, epidermal, cardiac, pulmonary, hepatic, osseous and renal. And the words stomach, artery, vein and tendon with their classical origin have supplanted the Anglo-Saxon originals, if there were

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†Director, Department of Gastroenterology, Lahey Clinic.

such. There were many classically derived synonyms for the Anglo-Saxon words *both* of which held their place and meaning, some of them being related to medicine: the Latin *cure* and the Anglo-Saxon *hele*, the Latin *perception* and Anglo-Saxon *knowledge*.

But let us now turn to the names of our profession and of those who practice it. The word medicine comes to us from the Latin *medicina*, the verb root of which is *mederi*, to heal, a thoroughly respectable derivation. But it has kinship with Medea, the enchantress — who was able to change an old ram into a lamb by cooking it in a cauldron and to restore an old man to youth by letting his blood and substituting a magical preparation. Was she the forerunner of the medicine man of early days, and in her practice was there a hint of the possible future range of endocrinology? And, finally, can she be designated as the first female in literature to practice the art, if not the science, of medicine? This word medicine, however, was in Old English lǣce crǣft ("Leech-craft"), indicating that medicine in those Anglo-Saxon days was largely limited to the use of leeches to suck out disease with blood. The word leech is the Middle English *leche* and actually meant a physician as well as a conjurer. In *Luke* IV:23, the sentence that we know so well as "Physician, heal thyself" is translated by Wycliffe as "Leech, heal thyself." We are left in doubt concerning why the physician was called "leech" — was the blood-sucking worm we call a leech named after the physician, or is that use of the word an epithet derived from the animal kingdom?

With the advent of the word medicine, the practitioner of the art was for a time called mediciner. In a manuscript, *Cardanus' Comforte* translated and published in 1573 by the Earl of Oxford, the man who, many believe, wrote the plays and poems attributed to Shakespeare, there is a reference to "the cunning and expert mediciner or physician." This word, however, came to have the second connotation of sorcerer. Today the root *medic* — to designate the physician — survives only in the Italian *medico*, used in English for the student of medicine, or colloquially in the plural medicos or medics for the profession.

The words that supplanted it, doctor, physician and surgeon, have interesting histories. They came directly from the so-called dead languages. That these dead languages still live is evidenced by their immortality in our inherited medical language and their rebirth in such modern words as radiology, geriatrics and psychoanalysis and a long list of others. In fact, the place of Greek in medicine is so gigantic that to paraphrase the words of a modern philologist "The medical lexicon is a trophy of Greece."

Doctor comes from the Latin *doceo*, to teach, and actually means the teacher and the learned man. The sorcerer and the medicine man have been replaced by the scholar, and in keeping with the high standards of our best medical societies, the practitioner of medicine has become learned and must impart his learning. Dr. Johnson, in 1775, said "The term doctor distinguishes him to whom it is granted as a man who has attained such knowledge of his profession as qualifies him to instruct others."

Physician also connotes a high principle of medicine, for its origin lies in the Greek word *physis*, which means "nature." The word physiology means nature lore. Galen says, "Greatest is the Physis and Hippocrates is its prophet." Both Galen and Hippocrates maintained the *unity* of the organism with its government by a *Physis* or *nature*. The physician or healer best fulfills his purpose by keeping or restoring the natural state of the creature. Perhaps the very derivation of the word physician conveys a subtle warning that in our treatment of the human being we avoid wherever possible interference with the *physis* or nature.

The word surgeon has a truly interesting history. The two roots of this word are Greek, "*cheir*" meaning hand and "*ergon*" work: he works with his hand. The *chirurgeon* became *surgeon* after a few centuries and a misspelling or two by medievals in France and England. The earliest practitioners of surgery combined two professions and were called barber-surgeon. There is also a humorous word chirotonsor, the Latin *tonsor* (from the verb *tondere*, to shear), he who shears by the hand — and he *really was* a barber. We will return later to this interesting combining form *chiro*.

The word medicine, unless used with a restricting adjective like veterinary or dental, is now understood to mean the science and art of healing the human body and mind. That word human, though containing the syllable man, an Anglo-Saxon word, is of course actually a derivative of the Latin *homo*. In passing it may be noted that the word woman comes from the Anglo-Saxon *wif-mann* — the wife human being — and wife may derive from Old Norman *Viſm*, meaning veiled — the veiled human. The person so described still wears a veil at times even though sometimes only a vestige of one. This reference to her wearing apparel is less derogatory than the implication in the word hysterectomy — derived from Greek *hysteria*, hysteria, indicating that women were the excitable sex. In the last century female and woman have exchanged dignity, the word female now being used chiefly in legal and medical parlance or at times in conversation and literature with perhaps a touch of cynicism or ridicule, while the word woman, once considered somewhat vulgar, now has both dignity and gentility.

Body is a straight Anglo-Saxon derivative from *bodig*, while mind has both Anglo-Saxon and Latin derivation in the Anglo-Saxon word *Gemynd* and the Latin word *mens* from which our adjective mental comes. As already stated the external parts of the body and the fundamental organs are defined

chiefly with Anglo-Saxon words. Face is an exception, this four-letter word coming from the Latin *facies* meaning form, shape or face.

Some parts of the body have names that describe their function or their shape or structure — for example, the following:

Lungs — a Teutonic word from Middle English *lunge* — meaning light and referring to the light weight of this organ, and surviving in the use of the word lights for the lungs of animals.

Stomach — the old French *estomac* — Latin *stomachus* and Greek *stomachos*, which in turn comes from *stoma* — the mouth. The earliest meaning of this word implied a "liking" — and we still say "I can't stomach him." We use a different Greek root, the word *gastron*, for the adjective and other derivatives such as gastric, gastrology and gastronomy.

The part of the stomach called the pylorus is picturesquely named from the Greek *pyle* and *ouros*, the keeper of the gate — a gate keeper that, as we all know, must be awake and alert but if neurotic about his job causes the familiar pylorospasm, with its original meaning, a convulsion of the gate keeper.

There is an interesting word *wame*, a form of womb, used in Scottish popular poetry to mean stomach, as in the line "food fills the wame and keeps us livin." In 1756 a Scottish traveler used the word a-wameling to describe the acute gastric distress and vomiting as well as staggering of seasickness.

Belly is from the Anglo-Saxon *belig* — which meant a bag or bellows and was in common usage in early times. In the Bible we find in *I Corinthians*, VI, "Meats for the belly and the belly for meats." Shakespeare, in his seven ages of man, mentions as the fifth age "the justice in fair round belly, with good capon lined," which for us modern mediciners sounds like a warning to *all* professions as well as the legal, against one of the dangers of middle age.

The words gut, bowel and intestine are respectively Anglo-Saxon, Middle English and Latin in derivation, all three being retained in modern medicine, with the Anglo-Saxon derivative gut now used in more colloquial medical parlance. Gut originally meant gutter from an Anglo-Saxon word meaning to pour. Bowel was in Middle English *bouel* and derived from the old French *boel* and Latin *botellus*, a little sausage, which in turn is a diminutive of *botulus*, sausage, from which we get botulism. The more dignified "intestines" has no other connotation except its simple meaning derived from the Latin meaning insides —coming originally from the preposition *intus*, meaning within. The word abdomen is of uncertain origin but is thought by some to be related to the Latin *abdere* to stow away, or hide — the place where things are stowed away or hidden. Others think it is akin to *adeps*, meaning fat.

Heart — Anglo-Saxon *heorte*, meaning life and the seat of life and strength as in the *Psalm* CIV: 15 — "Bread which strengtheneth man's heart." A hearty word this should be and is, with its many modern meanings ranging from heart, meaning "the muscular organ" that keeps us alive, to the term of affection as in "sweetheart."

Brain — the Anglo-Saxon *bragen* — meant originally the upper part of the head, and later the mass of nerve tissue enclosed by the skull or cranium — skull being an old Middle English word and cranium the Greek *kranion*. The word brain with an "s" added to it now means a combination of intellect and intelligence, but in the vernacular of the modern young it is kept singular, "the brain" being an epithet combining admiration and perhaps a touch of envy when applied to the smartest boy in the class. Strangely enough, as far as I can determine, this epithet is not generally applied to smart girls. Perhaps they prefer praise of the grace and beauty of their body to a suggestion that they are superintelligent. A part of the skull that we call the temple, with adjective temporal, has nothing to do with the religious structure but comes from the Latin *tempus* meaning time and interestingly enough indicates the area where the time of the body — that is the pulse rate — can be taken. This word temple is akin to temporary and with a stretch of the imagination can be conceived as providing a warning by the counting of the heart beat that time flies and in the words of Hippocrates "Life is short and art is long."

I cannot leave the brain area without mentioning to the brain surgeons who cut out pieces of the skull that the word trepan once had a more frivolous meaning. It was used to mean snare and the user of a snare. Burns says of the gay seducer in the *Jolly Beggars:*

> The ladies' hearts he did trepan
> My gallant, braw John Highland man.

Skin — an old Norse word has as its Latin equivalent the word integument. Here medicine has wisely kept to brevity, and while dermatology and dermatologists with their Greek derivations are used to designate the specialty and the practitioners in this specialty, we may still talk with dignity of the diseases of our skin and not of our integument or even of our derm. Interesting is the modern connotation of one's life or well-being as in the phrase to "save one's skin," a phrase justly based on the importance of the integrity of the skin.

The word muscle is the Latin *musculus*, which means a little mouse — a derivation nostalgic of our days in the physiology laboratory.

The limbs and their joints have some words of interest — arm is Anglo-Saxon arm or *earm*, but akin to the Greek *harmos* — meaning art — something fashioned with the arm. Later it came to mean power as indicated in the "arm of the law"

or "the arm of a baseball pitcher." Elbow comes from two Anglo-Saxon words *el*, meaning the length of arm, and *bow*, to bend. When we talk of bending the elbow, we are really bending the bend of the length of arm, a bit of tautology. Is this the origin of the word bender? Finger is related to the Middle English *feng* or prey — akin to *fang*, meaning something one uses to seize one's prey, a touch of atavism, no doubt. Hand is Anglo-Saxon of Teutonic and Norse origin, its scope of meaning having been enlarged, according to Webster, by thirty times its original meaning, including the round of applause and the bridge hand. Thumb is the Middle English *thombe* and originally meant the big or strong finger and akin to *tumere* — to swell — from which we have our medical word tumor. Although it is part of the approving hand in the phrase, "give the little girl a hand," this word thumb also has a derisive use in the phrase "to thumb one's nose." In speaking of hand I must come back again to that Greek combining form *cheir*. As we are so often reminded, the Greeks had a word for everything and from this word *cheir*, meaning hand, we got not only surgeon but also chiropractor and chiropractic, whose derivation is apparent enough, to designate the system of adjusting joints with the hand. Chirocosmetics is defined as the art of beautifying the hand — and if we were to prefer the Greek to Latin derivations we would have to say chirocosmetician instead of manicurist. We have been spared that as well as chirognomist in favor of the familiar palmist, but a very useful word in these days *would be* chirognomist, which is defined as knowing which hand, in other words, able to distinguish right from left. To be able to call a congressman chirognostic would be high praise in these days and might spare us much investigation, but of course the unlearned might regard it as a smear word.

Leg is a Middle English word *legge* and as such means what it means today but was once combined with arm in the word *armlegg* to mean arm. Its meaning is quite literal even though figurative when we say "he doesn't have a leg to stand on." I have not been able to determine accurately why the less specific word limb came to supplant leg in the prudish Victorian days. Foot is the Anglo-Saxon *fot* but the Greek *pous* with its combining form *pod* — has crept into our medical language. Chiropody from its two origins — *cheir* for hand and *pod* for foot — originally meant the treatment of both major and minor diseases of hands and feet — but is now restricted to the minor ailments, the chiropodist or more recently the podiatrist, being now only that ministering angel of healing sometimes ungratefully dubbed the corn doctor. And in passing, though somewhat irrelevantly, it may be noted that this use of the word corn comes from the Latin *cornu*, and indicates a horny substance; corn on the foot having no etymologic affinity with corn on the ear. The vertebras are strictly classic in derivation and accurate in meaning; they are the turners — from the Latin *vertere*, to turn. The bone and joint specialist knows that by fusion, which means literally pouring or blending together, he ignores the *physis* and *cures* by *destroying* a natural function. Wrist is also a turner coming from Anglo-Saxon *wrest*, meaning to turn, and originally was prefixed by the words hand and foot until the foot *wrest* got its own name ankle, an Anglo-Saxon word *ancleow*, meaning limb and claw. Toe is the Middle English *too* — meaning originally finger but in man and other bipeds applied to a digit of the hind or lower limb, whereas in quadrupeds it is used for the digits of all four limbs.

Before leaving the realm of orthopedics, let me mention the fact that that specialty is more properly as well as more simply called bone and joint diseases, — since orthopedic actually means straight child, — and if we are orthodox (that is, of straight opinion) we should use the designation of broader meaning to include the straight adult as well. The pedics in orthopedics is of the same derivation as *ped* in pediatrics and not that of *ped* in pedal or *pod* in chiropodist.

The word thyroid is from the Greek *thyreoides*, which means shaped like a shield, while uvula in Latin is a little grape and the Latin *tonsilla* comes from the verb meaning to clip or shear, a hint of tonsillectomies to come! The word artery has an interesting Greek origin, the Greek *arteria* meaning a windpipe that was supposed to carry the inspired air or pneuma all over the body. Trachea, which has its origin in a Greek word meaning rough, has survived to mean the main windpipe. Later, the artery was found to be filled with blood in the living human being and not air as in the dead, but the word was retained to mean blood vessel. Aorta derives from the Greek verb *aierein*, to lift or heave, and with the development of knowledge of the circulating apparatus came to mean the largest blood vessel that lifts the blood to the rest of the body. The capillaries are so named because they are as fine as a hair of the head, *capillus*. In antiquity the veins were confused with intestines and arteries, the word *veine* being an Old French word meaning a channel or river bed and probably derived from the Latin *vehere*, to convey.

But before we go too far with our more learned Latin derivatives that came into use with medical knowledge, let us revert once more to a good Anglo-Saxon word *lifer* from which we get liver — a well named organ without whose functions we cannot live. But it was not life alone that was associated with this organ; it was also regarded as the seat of passion and desire. A medieval Latin proverb says: It is the liver that makes one love. The word liverish has come to mean crabbed and melancholy while a *white*-livered person is a coward, an interesting play of color, for the words melancholy and melancholia refer, of course, to the *black* bile —

chole — that the liver secretes to make its owner depressed. Cholera has the same root, indicating the concept that it was a bilious disease. Color again is in the origin of the word cirrhosis (Greek *kirrhos* — meaning orange colored), a reference to the color of the diseased liver when sectioned. I suspect also that the original connotation of hypochondrium, which from its derivation means "under the cartilage of the breast bone," was a reference to the liver, the hypochondriac with his morbid anxiety about his health being chiefly concerned with that vital organ, the liver, or perhaps in a somatopsychic version *being* the hypochondriac because his liver is out of order. The word bilious and choleric also refer both the physical symptoms of headache, nausea and constipation and the irascibility and ill temper of the human being to a disturbance in the flow of bile (Latin *bilis* and Greek *chole*).

The word spleen has Greek origin (*splen*), and in addition to its designation of the organ, has for Shakespeare a meaning of laughter "Thy silly thought enforces my spleen" and for Wordsworth a meaning of melancholy. In modern usage it is often used to mean anger and malice.

Two structures have designations involving stories of ancient times: Achilles tendon or Achilles heel, meaning the vulnerable spot and referring to the story that Achilles' mother held him by his heel and dipped him into the Styx to make him invulnerable but missed the one spot covered by her hand. The other is the popular name for the prominent thyroid cartilage in the male, Adam's apple, referring to the folklore that when Adam took the forbidden fruit from Eve, a piece of it stuck in his throat, indicating that his physiology was better than his psychology.

The names of diseases for the most part developed with greater knowledge of disease processes. Some bear the names of the first observers of these processes as in Bright's, Addison's and many other diseases. Modern medicine with its background of literature and resources for research tends to disavow the honor of having one's name attached to a diseased condition by assiduously exploring the claim for such a distinction and usually turning up with evidence that some previous observer had described the condition at least in part. This was the case with regional enteritis, which Crohn first described to most of us and to which his name naturally and without his design was attached until someone came up with a reference to a previous description. Then it became terminal ileitis until objection was made that the word terminal suggested that it was a terminal disease and so regional ileitis was considered more appropriate. The word regional was doubly fortunate because later it became evident that the terminal ileum was not the only area of the small intestine to be involved, and for this reason the word enteritis was substituted for ileitis and the term regional enteritis now stands except that when the cecum is also involved it becomes regional enterocolitis. If we finally find that certain forms of phlegmonous gastritis are likewise the same disease, in the interests of accuracy we may have to enlarge the term to regional gastroenterocolitis. In these days we are more inclined to attach the names of the first observers or recorders to syndromes than to diseases. The list of these grows apace.

Accuracy in description and definition has become more and more the background of nomenclature of disease, but certain diseases will undoubtedly keep the names derived from an original picturesque background. Syphilis literally means friend of swine and was named for the hero of the description of the disease by the sixteenth-century poet and physician Fracastorius, who wrote "*Syphilis sive de morbo Gallico*," "syphilis or the French disease." The word lues, a Latin word, literally means plague (Latin *plaga* — a blow) and was formerly described as lues venerea when it meant syphilis. The word lues is now often used in an effort to conceal the whole bitter truth from the patient just as is the use of neoplasm and acid fast to mask cancer and tuberculosis. Malaria is *mala aria* — bad air, while diabetes comes from the Greek *dia*, through, and *baincin*, pour, a pouring through, referring to the polyuria of that disease. Migraine is the *hemi crania* — shortened to micrania and migraine, referring of course to the one-sided headache of that disease. The English have called it megrim with an additional meaning of low spirits and dullness. Diphtheria is thus named because of the false membrane formed during that disease likened to the Greek *diphtheron* meaning leather. Influenza is the Italian influence, an epidemic formerly attributed by astrologers to the *influence* of heavenly bodies. Quinsy throat gets its name from a choking dog (Greek *kyon*, dog, and *anchein*, to choke). Cancer comes from the Greek word meaning crab as demonstrated in its use for a sign of the zodiac but is akin to the Sanskrit word meaning hard referring to the hard shell of the crab. In its usual hard form and crab-like extension the disease fits both origins.

Patients often dub our nomenclature of disease double talk used in an effort to enhance the dignity of our efforts and the more cynical of them associate that dignity with higher fees. Excising a sebaceous cyst with its latinized terminology is, they say, a more expensive procedure than cutting out a wen.

Names of some diseases have been completely changed in meaning — for example, rheumatism, which derived from the old French *reume*, a cold, akin to the Greek word *rheum*, flow, which originally and to Shakespeare meant a cold in the head. The French still say *enrhumé* when they mean a person has a cold in the head, and the words diarrhea and catarrh have the same Greek root, *rhuo*, meaning flow. Later the word arthritis was attached to this

root rheum — to localize the cold to the joints so that when we designate the inflammatory joint disease as rheumatoid arthritis we are actually saying an inflammation of the joints (Greek arthron and the suffix that means inflammation *-itis*) resembling a cold in the head. The inaccuracy of this designation arose in part also because the suffix *-itis* was attached to the name of a structure to mean not only correctly diseases with inflammatory structural changes but also incorrectly *non*-inflammatory ones. We now have to use an adjective to distinguish between the functional conditions with their illegal terms, degenerative arthritis and functional colitis, and the inflammatory diseases of these structures legitimately named arthritis and colitis.

And in this connection it might be pertinent to call attention to the necessity for correct usage and spelling of the suffixes and prefixes so often used in medicine. *-Itis* meaning inflammation, as in bronchitis, should be distinguished from *-itus* meaning a state of, as in pruritus. The suffix *-osis* as in diverticulosis has come down to us to indicate the presence of diverticula as distinguished from diverticulitis, an inflammation in those diverticula. This word diverticulum, with its plural diverticula, is also an excellent example of the need for careful retention of the correct plural for Latin derivatives. We have taken them out of the Latin, and since we now have the resources of dictionary and literary editors and are no longer subject to the carelessness or ignorance of the copier of manuscripts, let us keep our borrowed words orthodox and for a neuter derivative ending in -um use the correct plural -a. The Greek prefix a- (a privative prefix — indicating negation) is used often in medicine as in the words anemia, aphasia, asepsis and achlorhydria, all of them taken right out of the Greek.

So far as disease is concerned, the word itself has a refreshingly uncomplicated origin, the destructive prefix Latin *dis-* denoting undoing, which takes all the ease out of ease, this word originally coming from Old French *aise*, meaning elbow room. We have to have elbow room to have ease and comfort, but disease undoes that pleasant sensation. We talk about both "pain" and the less painful "discomfort." These two words also have interesting derivations, pain being the Latin *poena*, the penalty one pays for disorders, and discomfort meaning the undoing of comfort, a Latin compound of *con* and *fortis* (*confortare* meaning to be strong and invigorated) indicating that comfort should be positive and of itself invested with strength and vigor. The word symptom comes from the Greek *symptoma* and means anything that has befallen one, coming from the Greek verb *sympiptein*, to fall together. Syndrome is likewise right out of the Greek *syn* and *dramein* to run with — that is, in Latin equivalent, a concurrence, a set of concurrent things.

An interesting symptom of disease is nausea — interesting, that is, in its derivation, for the word comes from the Greek *naus* meaning ship and of course refers to the kind of illness that with Dramamine has become almost obsolete. Sick is the Anglo-Saxon *seoc* and means ill and in British use is restricted to describing nausea and vomiting, while ill, an old Norman word *illr* of uncertain origin, describes any kind of disease and in Elizabethan times we had a noun *illth*, the antithesis of health. Vomiting and emesis are the Latin and Greek derivatives from words with the same meaning. Delirium comes from Latin *de*, off, and *lira*, furrow or track. In the slang of the gay '90's we went citified and said off the trolley instead of off the furrow.

In almost every branch of medicine now we are concerned with the toxic effect of three drugs commonly used in this age of Coca-Cola and cocktail parties. Coffee was described in 1624 by Francis Bacon as *caffa* (the Arabic form from the name of the Ethiopian province of Kaffa). Bacon called it "a drink, black as soot and of a strong scent, that comforteth the brain and heart and helpeth digestion." Tobacco originally meant a reed — *not* the weed — and referred to a Y-shaped pipe with which the Indians of the Antilles inhaled smoke through the nostrils. The sufferings of our patients denied the pleasures of this habit are pathetically described by Charles Lamb in his *Farewell to Tobacco*, in which he describes his loss of fellowship with the "*blest* Tobacco Boys" as follows:

> Where, though I, by sour physician
> Am debarred the full fruition [meaning enjoyment]
> Of thy favours, I may catch
> Some collateral sweets, and snatch
> Sidelong odours, that give life
> Like glances from a neighbour's wife.

The word alcohol has a most interesting derivation. Everyone has heard the drinker call his poison nothing but eyewash. Well by derivation that's what alcohol is — the Arab *al* meaning eye and the *kok'l* of Hebraic origin meaning to stain or paint. We also get kollyrium from this derivation, meaning originally a fine black powder for painting the eyelids.

The field of therapeutics is aptly named for that group of its progenitors, ancient ascetics called the *Therapeutae* — people who *served*. Among remedies used in this field, perhaps arsenic, calomel and paregoric have the most picturesque origins. Arsenic comes from the Greek *arren*, meaning the strong man, a rather poisonous tribute to masculine strength. Calomel is a "beautiful black" in its Greek origin so named because it is white though from a black mixture, and paregoric stems from the *agora* the turmoil of the market place, likened to the turmoil of the abdomen that must be soothed.

The word autopsy is a matter of seeing for oneself, and my list of words ends here except for a brief mention of two words with which medical societies

must often be concerned — quack and nostrum. Quack is a short form of the Danish word *Kwakzalver*, which has a literal meaning "one who boasts of his salves." It has become both a noun and a verb in English, as a verb meaning not only to quack like a duck but also "to make extravagant claims for" and as a noun "a boastful pretender to medical skill." The word nostrum is the Latin adjective "our" — in other words something "of ours" — a medicine, the ingredients of which are *our* secret and we won't tell.

Personal names are often an index to a nation's character and history. It is not uncommon to have grateful parents name a child for the doctor who helped him into the world, but unique is the use of the name of a disease for a child. However, Marco Pei in a delightful book, *The Story of English*, tells of an Oklahoma family who named their six children Tonsillitis, Appendicitis, Meningitis, Peritonitis, Phlebitis and Jakeitis, all familiar enough except the name of the youngest, whose name Jakeitis can only derive from a diseased condition induced by drinking Jake, a Jamaica-ginger extract. As I said before, our English language is never static.

Our vocabulary has grown from an estimated less than 100,000 Anglo-Saxon words to over 1,000,000 words in modern English, a goodly portion of which belongs to specialized fields including medicine. As English-speaking and English-writing doctors, we have therefore the responsibility and the privilege of expanding the English vocabulary, the largest in the world. We should do it both accurately and well.

The second part of this paper is to deal with epigrams. This Greek word literally means an inscription, but a common use of the word is in the sense of a bright or witty thought tersely expressed. Epigrams have served throughout the ages to express often in caustic phrase and always with precision and brevity the prevailing opinion, if not the wisdom of the maker of the epigram or the era in which he lived. Let us sample, therefore, what the ages of history have thought of our profession.

The idea that men do better without doctors and medicine was not born with Christian Science, as many epigrams testify. Hippocrates is the author of such maxims as the following: "Natural forces within us are the true healers of disease" and "To do nothing is sometimes a good remedy." In *Matthew* **IX**: 12, we read "They that be whole need not a physician," and Galen's wisdom was revealed in the sentence "The physician is only nature's assistant." Shakespeare in *Macbeth* says "Throw physic to the dogs; I'll none of it." And Oliver Wendell Holmes, in 1860, said, "I firmly believe that if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind — and all the worse for the fishes."

Time is recognized in modern medicine as a most useful handmaiden, and this was equally true in ancient times. Ovid, in the century before Christ, said very curtly, "Time is the best medicine," and in the sixteenth century we find the proverb "Patience is the the best medicine." In 1855 Bohn said, "Nature, time and patience are the three great physicians."

Modern precepts of health and hygiene are not as modern as we sometimes think. The values of rest, diversion and good diet were suggested frequently in epigrams throughout the centuries. In *Proverbs* **XVII**: 22, we read, "A merry heart doeth good like a medicine but a broken spirit drieth the bones." In more serious vein we find the avoidance of pride and sin lauded as preventing disease in *Proverbs* **III**: 7-8, where we read, "Be not wise in thine own eyes, fear the Lord and depart from evil. It shall be health to thy navel and marrow to thy bones." There is an old Irish proverb that in a characteristically Irish way says, "A good laugh and a long sleep are the best cures in the doctor's book."

We are justly proud of our knowledge of nutrition in these modern days, based as it is on chemical principles, calorie counting and food values, but the significance of correct diet and a preview of the age of vitamins and reduction diets are indicated in the following epigrams:

> The kitchen is a good apothecaries' shop — William Bullen in 1562.
>
> Feed by measure and defy the physician — John Heywood in 1546.
>
> Kitchen physic is the best physic — Jonathan Swift in 1738 [and I need hardly comment that here, of course, physic means the practice of medicine — not a laxative].

The English proverb — "An apple a day keeps the doctor away" — is without date, but it was said long before we knew much about vitamin deficiency.

In 1869 H. S. Leigh composed a quatrain, truly interesting to the modern doctor concerned with nutrition,

> If you wish to grow thinner, diminish your dinner
> And take to light claret instead of pale ale,
> Look down with an utter contempt upon butter,
> And never touch bread till it's toasted or stale.

And in 1640 George Herbert proclaimed, "A little with quiet is the only diet," thereby stipulating the two requisities for good digestion that we regard so highly today, serenity during meals and eating with moderation. Two English proverbs are of interest here. "A full belly neither fights or flies well" (1640) and "Full bellies make empty skulls." We also have from George Pettie in 1581, "A full belly doth not engender a subtle wit." The importance of quiet, that therapeutic state so much needed and so difficult of attainment in this modern world, has long been recognized as an effective curative agent. In association with meals it is advised by Burton in a footnote to the *Arabian Nights* (Volume V, page 222) where we find "After the noon meal, sleep, Although for moments twain, After the night meal walk, Though but two steps

be ta'en," a bit of advice propagated also in the homely couplet, "After dinner rest a while, After supper walk a mile." Excellent hygiene, as I'm sure we all agree.

Addison, in 1771, said, "Physic [that is, medicine] for the most part is nothing but the substitute of exercise or temperance." The *Regimen Sanitatis Salernitanum* of 1607 combines three essentials of good hygiene in the advice: "Use three physicians still: first, Dr. Quiet; next, Dr. Merryman, and Dr. Dyet." This advice was repeated a century later by Jonathan Swift when he said the best doctors in the world are Doctor Diet, Doctor Quiet and Doctor Merryman. Can modern hygiene or psychiatry improve upon these principles of rest, diversion and proper diet?

The penalties for violating these rules were emphasized in 1670 by John Ray, who said, "Diseases are the interests of pleasures." Josh Billings, in 1897, wrote, "Disease is the whipping post and branding iron of luxury."

The treatment of disease in 1780 was indicated by the anonymous statement of that period,

> When peoples' ill, They come to I,
> I physics, bleeds and sweats 'em,
> Sometimes they live, sometimes they die,
> What's that to I? I lets 'em.

Small wonder that the author's name is not appended.

Radical treatment of disease is justified by Hippocrates, "Extreme remedies are very appropriate for extreme diseases," a principle that was echoed in an English proverb of 1539, "Desperate diseases require desperate remedies" and by Shakespeare in *Hamlet*, "Diseases desperate grown, By desperate appliance are relieved, Or not at all."

For the physician himself, history in the form of epigrams has both good and evil to say. In *Jeremiah* VIII: 22, it is asked, "Is there no balm in Gilead; is there no physician there?" — a tribute to our curative power.

In 1638 Francis Quarles said, "Physicians, of all men, are most happy: Whatever good success soever they have, the world proclaimeth, and what faults they commit, the earth covereth." The author was, of course, unfamiliar with both staff meetings and suits for malpractice.

Voltaire blows hot and cold in his regard for our profession. He says, "Doctors are men who prescribe medicine of which they know little to cure disease of which they know less in human beings of whom they know nothing." But he makes amends for that cynicism in *A Philosophical Dictionary* by saying: "But nothing is more estimable than a physician who, having studied nature from his youth, knows the properties of the human body, the diseases which assail it, the remedies which will benefit it, exercises his will with caution and pays equal attention to the rich and poor."

For the surgeon, proverbs and epigrams have both praise and cynicism. In 1604 Marston says, "A pitiful surgeon makes a dangerous sore." In 1670 an English proverb says, "A good surgeon must have an eagle's eye, a lion's heart and a lady's hand." Martin H. Fischer, with the physiologist's love of nature intact, has unkind things to say of the surgeon: "A good surgeon is a good medical man who can cut. Most of the surgeons have forgotten their medicine but go right on cutting. . . ." And this same cynic proclaims, "The practice of medicine is a thinker's art, the practice of surgery a plumber's," and "Surgery is the cry of defeat in medicine." It would be interesting to know whether this same physiologist ever cried for help from a surgeon. One of our greatest surgeons, Will Mayo, said with truth often recognized, "It is not surgery that kills people: it is delayed surgery."

The problem of medicolegal jurisprudence has been treated in various ways throughout the history of the world. Even as far back in history as 1800 B.C. the Babylonian Hammurabi ruled in his legal code: "If a doctor operate on a man for a severe wound with a bronze lancet and cause this man's death, or open an abscess in the eye of a man with a bronze lancet and destroy the man's eye they shall cut off his fingers." Surgical risk in those days involved the operating surgeon as well as the patient.

The call to medicine was aptly defined by Billroth when he said, "The pleasure of a physician is little, the gratitude of patients is rare, and even rarer is material reward but these things will never deter the student who feels the call within him." The self-sacrifice of our profession is also subtly extolled by James Bryce, who in a speech in New York in 1914 said, "Medicine is the only profession that labors incessantly to destroy the reason for its own existence."

And speaking of material reward, the Hebrew Thesaurus, the *Talmud*, states that a physician who demands no fee is worth none. Daniel Defoe described a human foible familiar to all of us when he said:

> Frightened patients when they want a cure
> Bid any price and any pain endure;
> But when the doctor's remedies appear
> The cure's too easy and the price too dear.

Our own Benjamin Franklin, perhaps in a moment of spleen, said "God heals and the physician takes the fee."

Poets and philosophers of all ages have chanted paeans of health, all of which might be crystallized in the statement of Herophilus made three hundred years before Christ: "To lose one's health renders science null, art inglorious, strength unavailing, wealth useless and eloquence powerless." But the complaints of our patients against restrictions to preserve health were curtly stated by La Rochefoucauld in 1665 in the sentence: "It is a boresome

disease to try to keep health by following a too strict regimen."

The protagonists of exercise as a contributing factor to health are found in early days as shown by James Thomson's:

Health is the vital principle of bliss
And exercise, of health.

For those of us who are practicing the new specialty of geriatrics in the subjective as well as objective sense there is comfort in the statement of Thomas Fuller, made in 1642, "Commonly, physicians, like beer, are best when they are old."

And with this note of cheer to the elder generation of doctors I will bring to a conclusion this "literary composition, intentionally slight in treatment, discursive in style and familiar in tone." But not without quoting the seventeenth-century epitaph that any one of us would be proud to wear upon our tombstone — the one written by William Browne on Mr. Vaux, the physician:

Stay! This grave deserves a tear
.....
Tis Vaux whom Art and Nature gave
A power to pluck men from their grave;
When others' drugs made ghosts of men
His gave them back their flesh again;
Tis he lies here, and thou and I
May wonder he found time to die;
So busied was he, and so rife
Distributing both health and life.

And finally that always inspiring epigram of Hippocrates, "Wherever the art of medicine is loved, there also is love of humanity."

THE USE OF DIAMOX, A CARBONIC ANHYDRASE INHIBITOR, AS AN ORAL DIURETIC IN PATIENTS WITH CONGESTIVE HEART FAILURE*

CHARLES K. FRIEDBERG, M.D.,† ROBERT TAYMOR, M.D.,‡ JAMES B. MINOR, M.D.,§ AND MARK HALPERN, M.D.§

NEW YORK CITY

IT would be highly desirable to obtain a diuretic agent that could be given orally and yet act as effectively as parenterally administered mercurial diuretics, without producing significant toxic manifestations. The xanthine diuretics,[1, 2] chemically related uracil derivatives[3, 4] and other preparations of mercurials[5, 6] have been ineffective, inconstant in effect or associated with unpleasant side actions or toxicity. Recently, additional mercurial diuretics for oral administration have been tested in patients with heart failure.[7-9]

Another approach to the development of a satisfactory oral diuretic is based on the observation that inhibition of carbonic anhydrase activity in renal-tubule cells not only impairs the tubular secretion of hydrogen ion[10] but also diminishes the retention of sodium, a major objective of diuretic therapy in heart failure. Since the sulfonamide compounds were found to be specific carbonic anhydrase inhibitors,[11] Schwartz[12] administered sulfanilamide to 3 patients with congestive heart failure and reported a diuretic effect.

Although sulfanilamide has a relatively weak effect and is too toxic for prolonged or widespread usage, other sulfonamide compounds[13] have been found to be more active carbonic anhydrase inhibitors without the toxicity of sulfanilamide.[14] One of these, compound 6063 (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide), now known as Diamox, is fifty to four hundred times as potent a carbonic anhydrase inhibitor as sulfanilamide.[14] The prolonged administration of large doses of Diamox to rodents, dogs and monkeys has not resulted in toxic manifestations.[15] The intravenous administration of a single dose of Diamox to animals[16] and to human subjects[17] with and without heart failure caused a large increase in the excretion of sodium. Therefore a study was undertaken of the possible usefulness of Diamox¶ as an oral diuretic in patients with congestive heart failure. Moderate diuretic effects were noted in 15 edematous patients after oral administration of a carbonic anhydrase of unstated composition.[18]

MATERIALS AND METHODS

The clinical material is presented in Table 1. Twenty-six patients were studied, 15 men and 11 women ranging in age from thirty-six to seventy-six years. Eleven patients had coronary-artery disease, 7 had hypertensive and coronary-artery disease, 7 had rheumatic heart disease, and 1 had syphilitic heart disease. Eleven patients were hospitalized during the period of study; the remaining 15 were ambulatory and were followed in the outpatient department. These two groups are discussed separately.

Hospitalized Patients

The first group consisted of 11 patients admitted to the hospital for treatment of congestive heart failure. Hospital admission was necessitated by the uncontrolled and increasing severity of the clinical

*From the Department of Medicine, Mount Sinai Hospital.

†Assistant professor of clinical medicine, Columbia University College of Physicians and Surgeons; associate attending physician, Mount Sinai Hospital.

‡Research assistant in medicine, Mount Sinai Hospital.

§Research assistant in medicine, Mount Sinai Hospital; Damian Medical Foundation research fellow.

¶Kindly supplied by the Lederle Laboratories, New York City.

manifestations despite various therapeutic measures. The classic signs and symptoms of heart failure were present in all these patients, and the arm-to-tongue circulation time was increased. The venous pressure was increased or rose above normal after abdominal pressure (positive hepatojugular reflux).

A complete physical examination was made on admission, with special reference to the individual symptoms and signs of heart failure, which were graded according to severity and recorded daily. Immediately after admission one or two twenty-four-hour control urine specimens were obtained, depending on the urgency for beginning diuretic therapy. In 1 patient (D. G.) the need for therapy was regarded as so urgent that Diamox was administered without a control urine. Rest in bed, the dietary restriction of sodium to 500 mg. daily and the administration of digitalis were maintained uniformly in all patients throughout the period of study.

Diamox was administered every eight hours to 6 patients until no further response was obtained or toxic symptoms developed. As a rule the drug was continued for three or four days, but in 1 case it was continued for five days. The remaining 5 patients received the drug every eight hours in courses lasting from one to three days. This dosage schedule was based on previous observations that the effects of a single dose of the drug lasted up to eight hours and that effectiveness with continued dosage diminished each day and was minimal after three days. Four patients received mercurial diuretics by injection at some time during the period of observation.

During the study the patients' weight and the presence and severity of the individual symptoms and signs of congestive heart failure were observed each day. Frequent blood specimens were obtained and analyzed for sodium, potassium, chloride and carbon dioxide content of the plasma and the pH of the blood. All urine specimens were collected at intervals of four or twenty-four hours and analyzed for sodium, potassium and chloride.

Outpatients

The ambulatory group consisted of patients who had been undergoing treatment for chronic congestive heart failure in the cardiac clinic. These patients were said to require and had been receiving parenteral mercurial diuretics at intervals of two to seven days. When a patient was first seen, a complete history was taken, and physical examination, roentgen-ray examination of the heart, electrocardiographic studies, complete blood count, urinalysis and blood urea nitrogen determination were carried out. Activity, diet and digitalis intake were not changed. Every patient was instructed to record his daily weight in a small notebook that was brought to the clinic at each visit. During the initial (control) observation period, mercurial diuretics were administered intramuscularly as required, and the effect on symptoms, physical findings and weight was noted. An effort was made to omit the mercurial injections or to prolong the intervals between injections. After elimination of patients who were found not to require mercurial diuretics or who required mercurial injection very infrequently, Diamox was administered to those

TABLE 1. *Diuretic Effect of Orally Administered Diamox.*

PATIENT	URINE VOLUME		WEIGHT LOSS	CLINICAL RESPONSE	POTASSIUM EXCRETION		SODIUM EXCRETION		CHLORIDE EXCRETION	
	CONTROL cc./day	DIAMOX cc./day	lb.		CONTROL milliequiv./day	DIAMOX milliequiv./day	CONTROL milliequiv./day	DIAMOX milliequiv./day	CONTROL milliequiv./day	DIAMOX milliequiv./day
Hospital patients:										
D. G.	—	1380	8.0	Excellent	—	64	—	268	—	183
G. L.	2000	4724	6.5	Excellent	38	94	144	332	139	211
M. M.	1320	1853	3.8	Good	44	64	46	73	54	37
C. P.	580	1700	2.8	Good	22	69	7	98	32	49
H. L.	1790	1879	3.5	Good	114	173	70	171	37	49
J. S.	902	1390	3.5	Good	86	203	1	51	1	2
E. S.	760	1492	5.0	Good	20	36	41	146	53	81
J. N.	1350	1995	8.5	Good	28	35	40	99	67	60
S. W.	1172	1720	4.0	Good	42	93	8	61	3	15
N. B.	1312	1968	2.0	Poor	52	99	1	1	31	15
C. S.	390	765	1.5	Slight	21	63	3	46	3	3
Outpatients:										
T. B.	715	1452	4.0	Excellent	38	119	89	175	73	141
M. M.	1290	1900	8.0	Excellent	38	93	162	346	169	171
F. T.	560	1685	4.0	Good	62	106	68	170	68	93
L. S.	1045	1275	4.0	Good	33	42	46	126	83	66
H. F.	952	1575	3.0	Good	40	50	125	209	116	112
C. N.	620	1040	2.5	Good	28	52	34	99	38	22
L. B.	1000	1700	3.0	Good	71	131	68	196	91	93
S. S.	1635	2305	4.0	Good	55	75	84	178	150	98
C. G.	635	1200	1.5	Good	28	40	55	176	20	56
P. S.	893	1150	1.0	Poor	62	154	5	95	4	7
S. B.	940	1820	2.0	Poor	42	160	37	92	24	68
A. G.	2333	1975	0	None	21	17	84	106	97	98
R. T.	555	1040	0	None	20	71	1	15	2	3
A. B.	380	358	0	None	21	30	8	27	7	12
J. L.	260	235	0	None	11	21	0	3	0	0

who required mercurial injections at intervals of ten days or less for control of the heart failure.

Of 26 patients originally referred for study, only 15 were considered suitable for investigation. When the mercurial requirement for each patient had been established, Diamox was given orally, and the mercurial injection was administered only if the signs and symptoms of congestive heart failure were not controlled. Diamox was given three times a day in courses that lasted from one to three days but usually for two days. Courses were repeated every two to seven days (in most cases every seven days). The individual dose varied from 0.25 to 0.75 gm. In addition, 6 patients were each given a single dose of 0.25 gm. of Diamox daily for seven days. A placebo was administered to 4 patients at some time during the period of study. Two patients who had received Diamox were given 8.0 gm. of ammonium chloride a day for two days for comparison of its effect with that of Diamox. Twenty-four-hour urine specimens were obtained for two days before and for two days during the initial administration of Diamox, and these specimens were analyzed for sodium, potassium and chloride. Blood specimens were obtained at the beginning and at the end of the first course of Diamox and analyzed for sodium, potassium, chloride, carbon dioxide content and pH.

Blood was obtained from the antecubital vein, specimens for carbon dioxide content and pH being drawn into a greased syringe containing sodium fluoride and heparin. Urine specimens were spontaneously voided and collected in a bottle containing mineral oil and thymol.

Sodium and potassium levels were determined by a Janke flame photometer, with the use of lithium as an internal standard. Chloride was determined by the method of Schales and Schales.[19] Plasma carbon dioxide content was determined manometrically according to the method of Van Slyke and Neill,[20] and pH was determined with a glass electrode and a Cambridge Research pH meter.

Results

Effects of Intravenously and Orally Administered Diamox

Figure 1 shows the differences in rates of water and sodium excretion in the same patient after the administration, as a single dose, of 0.75 gm. of Diamox intravenously and, one week later, 0.75 gm. of Diamox orally. The onset of action of the drug was thirty minutes earlier after intravenous than after oral administration. Higher rates of both water and sodium excretion were obtained after the intravenous administration of Diamox, but oral administration of the drug produced a fairly rapid and significant rise in water and sodium excretion. A maximum urine flow of 10 cc. per minute was attained thirty minutes after the intravenous injection of Diamox, whereas a maximum flow of 8 cc. per minute occurred ninety minutes after the oral dose. When a similar ninety-minute interval was permitted to elapse, sodium excretion rose from 6 microequiv. to 120 microequiv. per minute after intravenously administered Diamox, and from 1.6 microequiv. to 59.6 microequiv. per minute after orally administered Diamox.

Effect on Water Excretion

Since no attempt to control the fluid intake of these patients was made, the changes in water excretion (Table 1) cannot be fully evaluated. However, the twenty-four-hour urine volume increased in all but 3 patients after oral administration of Diamox. The range of increments for a twenty-four-hour period varied from 100 to 2724 cc., the mean increment for the group being 704 cc. The 3 patients who had no increase in urine volume also showed no clinical improvement after Diamox.

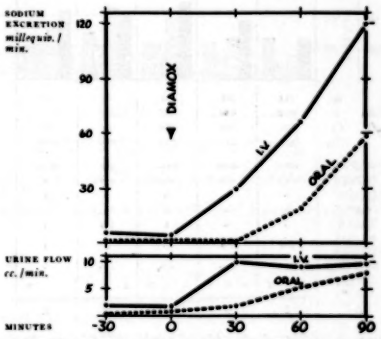

FIGURE 1. *Effect on Water and Sodium Excretion of the Administration of a Single Dose of 750 Mg. of Diamox Intravenously and, One Week Later, 750 Mg. Orally to the Same Patient.*

Effect on Electrolyte Excretion

Sodium. The rate of sodium excretion increased in all subjects after Diamox regardless of the diuretic response. However, in patients in whom a satisfactory diuresis was obtained the increments in sodium excretion after a single course of Diamox varied from 37 to 188 milliequiv. for a twenty-four-hour period. The mean increase for this group was 90 milliequiv. In the group of patients in whom the resultant diuresis was insufficient to control the heart failure, the increments in sodium excretion over a twenty-four-hour period varied from 1.0 to 90 milliequiv., with a mean of 31 milliequiv. (Table 1).

Potassium. Excretion of potassium after the administration of Diamox increased in all patients except 1. There did not appear to be any relation between changes in potassium excretion and clinical response to the drug. In the patients in whom the diuresis was considered satisfactory, the range of increments of potassium excretion was 10 to 117 milliequiv. for a twenty-four-hour period, with a mean of 43 milliequiv. In the unresponsive group, the increments for a twenty-four-hour period ranged from 10 to 118 milliequiv., with a mean of 51 milliequiv.

Chloride. The effect of Diamox on chloride excretion was variable. In 16 patients slight to moderate increases were noted, whereas in 8 the rate of excretion fell. The changes for a twenty-four-hour period varied from a decrease of 52 to an increase of 72 milliequiv.

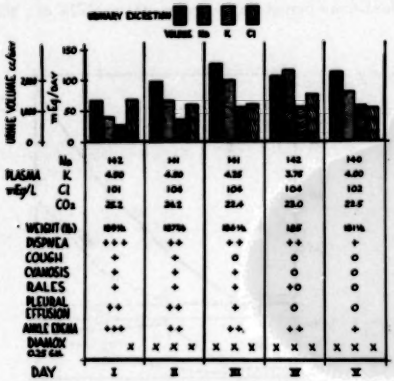

FIGURE 2. *Effect of the Administration of Diamox Every Eight Hours on Water and Electrolyte Excretion and in Weight and Clinical Picture of Hospitalized Patient J. N.*

Effect on Plasma Electrolytes

There were no significant changes in plasma levels of sodium, potassium or chloride after the administration of Diamox to these patients. The carbon dioxide content of plasma fell in most cases after the drug, and in some this was accompanied by a slight fall in the blood pH.

Effect on Body Weight and Clinical Response

All the hospitalized patients lost weight after the oral administration of Diamox (Table 1 and Fig. 2). The range of weight loss in this group after a single course of Diamox was 1.5 to 8.5 pounds, with a mean of 4.4 pounds. These weight losses occurred during a period of therapy lasting three or four days in 8 cases, and six, five and one day, respectively, in each of the other 3 cases. Nine of these patients experienced sufficient improvement in clinical signs and symptoms after receiving Diamox to make the additional use of parenteral mercurial diuretics unnecessary (Table 1). The remaining 2 patients had little or no clinical response, and mercurial diuretics were required.

Four of the ambulatory patients lost no weight after the administration of Diamox. The weight losses in the remaining 11 after a single course of Diamox varied from 1.0 to 8.0 pounds, the mean decrease for these patients being 3.4 pounds. These losses occurred over a two-day period in 10 patients, over a three-day period in 4 and over a four-day period in 1. The clinical response in 9 patients was considered to be satisfactory in that signs and symptoms of congestive heart failure were controlled by the administration of Diamox at least as well as they had been with the use of parenteral mercurial diuretics. In these cases Diamox could be satisfactorily substituted for the injection of mercurial diuretics. The remaining 6 patients showed an unsatisfactory clinical response, and it was necessary to resume the administration of mercurial diuretics.

After it had been demonstrated that Diamox was incapable of producing a satisfactory diuresis in these patients, 3 of them (S.B., A.G. and A.B) were given repeated mercurial injections until a minimum or "dry" weight was obtained. Diamox was then given orally in an attempt to prevent a reaccumulation of fluid. In these 3 patients, the Diamox did not influence the rate of weight gain. J. L., another patient with an unsatisfactory therapeutic response, had marked ascites and ++ edema of the lower extremities. Neither mercurial diuretics nor Diamox produced a diuresis, and an abdominal paracentesis was necessary. Immediately afterward, Diamox was started in a dosage of 0.25 gm. daily. No gain in weight occurred until a placebo was substituted for the Diamox, when the patient gained 7 pounds in a period of nine days on the placebo. With resumption of a course of Diamox he lost 3 pounds but had to have an abdominal tap again because there appeared to be no diminution in the quantity of ascites.

Effect of Continuous Diamox Administration

When 0.25 gm. of Diamox was administered every eight hours for three or more days, there was a gradual diminution of effect in terms of the excretion of water, sodium and potassium. The maximum increase in excretion rates of these substances usually occurred during the first or second twenty-four hours after the initial dose of the drug. On the succeeding days the excretion rates gradually fell until they reached the control levels. This

usually occurred by the third or fourth day. It was necessary to discontinue the drug for at least forty-eight hours before a renewed response could be elicited.

When 0.25 gm. of Diamox was given only once a day continuously, no diminution in effect was noted. In the patients who responded satisfactorily to Diamox, diuresis and weight loss occurred until a minimum weight was reached. Thereafter weight and the signs and symptoms of congestive heart failure reappeared or increased in severity (Fig. 3).

Comparison with Ammonium Chloride

Since Diamox produces some acidosis, the possibility that the acidosis accounted for the diuretic effect was considered. The diuretic effect of Diamox was therefore compared with that of ammonium chloride. Two patients, T. B., and F. T., who

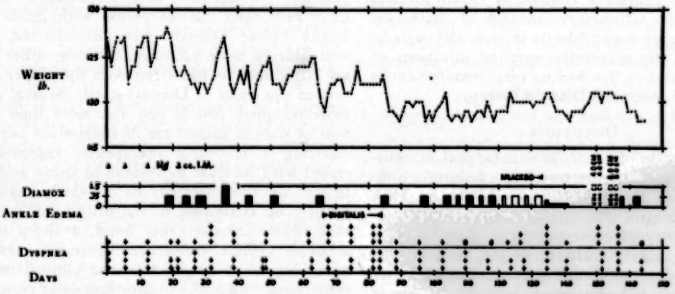

FIGURE 3. *Effect of Intermittent Diamox Administration over an Extended Period to Ambulatory Patient T. B.*

Also shown are the results of placebo and ammonium chloride administration and, initially, of Mercuhydrin.

gain due to retention of water was prevented as long as the Diamox was continued.

Effective Dosage Level

In the ambulatory group of patients, 0.25, 0.5 or 0.75 gm. was utilized as the single dose to be taken three times a day in courses lasting two or three days. When the drug was to be taken once a day continuously, 0.25 gm. was utilized as the single dose. Variations in the dose in the same patient did not appear to alter the clinical response. Patients who did not respond to smaller doses did not have a diuresis with a larger dose, nor did prolongation of the course beyond two days have a result in these patients. The most advantageous effective dosage schedule in this series of patients appeared to be 0.25 gm. three times a day for two days, with courses repeated every two to seven days, or the continuous administration of 0.25 gm. of Diamox once daily.

Effect of Placebo Administration

Four ambulatory patients were given a placebo instead of Diamox at some time during the study. All these patients had responded to Diamox, and the symptoms of congestive heart failure had been satisfactorily controlled. When the placebo was administered, the patients began to gain weight had responded well to Diamox were given 8.0 gm. of ammonium chloride daily for two days. Although a slight acidosis developed and there was an increase in sodium and chloride excretion in both patients, no weight loss or clinical improvement followed the ammonium chloride (Fig. 3).

Toxicity

No serious toxic manifestations were noted in any of the patients in this series. The mild acidosis was not accompanied by any of the typical signs or symptoms. The most frequent side action encountered was mild drowsiness, which occurred in 6 patients when Diamox was administered every eight hours in courses of two or three days. Four of the 6 patients who received Diamox daily for one week or longer also complained of some drowsiness and lassitude. These complaints disappeared promptly on discontinuance of the drug. Four patients complained of mild "tingling" sensations in the fingers. This symptom was also transient. Neither the drowsiness nor the paresthesias were of sufficient degree to warrant discontinuance of the drug when it was employed in the dosage schedules described above. Five of the ambulatory patients continued to receive Diamox, on the interrupted schedule, for over two months.

No evidence of renal damage or hemopoietic disturbance was observed.

Two patients (T. B. and S. S.), who received 0.25 gm. of Diamox three times daily for two days each week over a period of six months, have not required mercurial diuretics and have remained at their basal weight and free of cardiac symptoms except for moderate exertional dyspnea (Fig. 3). However, after six months of therapy they have begun to complain of lassitude and moderately severe anorexia. Another patient, F. T., who has received weekly courses of Diamox by mouth for four months, with satisfactory control of both his weight and symptoms of heart failure, although he discontinued the previously required injections of mercurial diuretics, has had no toxic manifestations as a result of continued Diamox therapy.

Discussion

The evaluation of a new diuretic for oral administration in cases of congestive heart failure is difficult because it is not always possible to establish satisfactory control observations or to exclude other factors that may influence the effects being studied. Changes in urinary output, weight, urinary excretion of sodium and clinical manifestations after administration of Diamox were the essential criteria utilized to assess the effectiveness of this drug.

Despite uncontrolled water intakes and absence of water-balance studies, it is of interest that the twenty-four-hour urine-volume output increased after Diamox therapy in 23 of the 26 patients studied, the average increment being 78 per cent of the control values. That these figures are significant appears to be supported by concomitant changes in weight and in clinical manifestations and in sodium excretion. Careful determinations of the daily weights serve as a fairly reliable index of changes in water balance from day to day. A significant weight loss occurred in all the patients who appeared to have a diuresis after Diamox as determined by the urinary volume, whereas there was no loss of weight in the 3 patients in whom there was no increase in twenty-four-hour output of urine. Similarly, each of the cardinal symptoms and signs of congestive heart failure was specifically evaluated, graded and recorded, and a comparison made before and after Diamox administration. These observations also showed that distinctive clinical improvement after Diamox occurred in patients in whom there was also an increase in urinary output and a loss of weight, and that there was no clinical benefit in patients who exhibited neither diuresis nor weight loss. Sodium excretion increased in all patients after administration of Diamox. The 4 patients who had the least increase in sodium excretion experienced no clinical improvement, and 3 of these had no increase in urinary volume. The consistent correlation between increased urinary output, weight loss, increased sodium excretion and clinical improvement enhanced our confidence in the validity of each of these observations, despite the difficulty in obtaining satisfactory controls or complete balance studies. Finally, the use of a placebo likewise supported the significance of the data obtained, for in no case was the placebo followed by an increase in urine volume, weight loss, increase in sodium excretion or clinical improvement such as followed administration of Diamox.

For detailed balance studies in the hospitalized patients it would have been preferable to obtain a more prolonged control period with fixed sodium intake before Diamox was administered. However, during more prolonged periods, other factors are introduced that interfere with the proper evaluation of the effect of Diamox itself. Several days of more complete rest in bed and more rigid restriction of sodium intake are in themselves capable of inducing a favorable therapeutic response associated with increase in volume of urine and quantity of sodium excreted, all of which might erroneously be attributed to the drug administered at that time. On the other hand, a sharp increase in urine volume and sodium excretion associated with significant weight loss and clinical improvement, occurring in the twenty-four-hour period after administration of Diamox, which in turn followed only a twenty-four-hour control period, was much more likely to be the result of the drug than of any other change in therapeutic management. The one-day or two-day change in sodium intake from 2 to 3 gm. of sodium at home to 500 mg. in the hospital is ordinarily followed by a corresponding reduction in sodium output, even when the net balance is more favorable for the patient with heart disease. Therefore, the increase in sodium excretion despite the reduction of sodium intake in our patients is interpreted as an effect of the Diamox.

Although the administration of Diamox is followed by acidosis, the acidosis observed in this study appeared to be minimal and was probably not a significant factor in determining the diuresis and other clinical features. Our observations were limited to only 2 patients, but the failure of ammonium chloride to produce a diuresis in patients who responded well to Diamox also indicates that the acidosis was not a major factor in these cases.

When a single dose of Diamox is administered, its action is largely completed in four or five hours and entirely completed in eight hours. With continued administration every eight hours, each dose is again effective, but to a lesser degree. After two or three days of this dosage three times in each twenty-four hours, the drug loses its activity completely or partially. This may result from loss of sensitivity to the inhibitory effect of the drug by the carbonic anhydrase system or from local tubular or general metabolic adjustments. If the drug is given only once daily, this refractoriness does not

appear in spite of continued administration. Refractoriness may therefore be avoided either by a drug-free interval after its continuous administration every eight hours for two days, or by a drug-free interval each day with only one dose daily. This applies to any effective dose from 0.25 to 0.75 gm. — the higher dose did not appear to be more effective than the lower.

Eighteen of the 26 patients studied showed a clinical response that compared favorably with that after parenterally administered mercurial diuretics. In general, a favorable clinical response accompanied a corresponding, significant weight loss. However, patients who had only or predominantly left-sided heart failure improved considerably with the loss of relatively small amounts of edema fluid from the lungs.

It is possible that failure of absorption of Diamox from the intestinal tract accounts for lack of diuresis in some patients. This was investigated in patient A.B., who did not experience a diuresis after oral administration of Diamox. After the administration of a single dose of the drug to this patient, the urine was examined for carbonic anhydrase inhibitor activity. Seventy-two per cent of the administered drug was recovered in the first twenty-four hours,* lack of absorption being thereby excluded as a factor in the therapeutic failure.

No serious toxic side actions were noted in these patients when the dosage schedules described above were employed. Drowsiness, lassitude and paresthesias occurred but disappeared promptly when the drug was discontinued. In no case was it necessary to abandon the drug because of side actions. But it may be desirable to interrupt therapy for a few days or to utilize intermittent administration in short courses instead of continuous administration in patients who exhibit any unpleasant effects of the drug. Despite the potassium diuresis induced by Diamox, observations in this series of cases indicate that there is little danger of potassium depletion when the drug is given intermittently, periods of recovery between courses being allowed. However, further observations are necessary to determine whether significant potassium or other electrolyte depletion occurs when Diamox is administered continuously for long periods.

*Analysis carried out through the courtesy of Dr. Thomas Maren, American Cyanamid Corporation, Stamford, Connecticut.

Summary

The carbonic anhydrase inhibitor, Diamox, was employed as a diuretic for oral administration in 26 patients with congestive heart failure.

Diamox prevented the secretion of an acid urine and promoted the excretion of sodium and potassium.

Eighteen patients demonstrated diuresis, weight loss and clinical improvement after the oral administration of Diamox that compared favorably with those after a mercurial diuretic given parenterally.

Toxic side actions were unimportant in the patients studied and those that did occur did not necessitate discontinuance of the drug.

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MASSIVE MESENTERIC INFARCTION FOLLOWING INFERIOR MESENTERIC-ARTERY LIGATION IN RESECTION OF THE COLON FOR CARCINOMA*

ROBERT S. SHAW, M.D.,† AND THOMAS H. GREEN, JR., M.D.‡

BOSTON

THE importance of resecting the entire inferior mesenteric chain of lymph nodes with carcinomas of the descending and rectosigmoid colon, originally stressed by Moynihan[1] in 1908, has recently received attention in the surgical literature.[2,3] It has been recommended that resection of these lesions be routinely accompanied by division of the inferior mesenteric artery at the aorta to permit a complete removal of regional lymphatics and lymph nodes with the primary growth. It is the purpose of this paper to report a complication that followed this technical step in such a resection and to suggest means for its avoidance.

CASE REPORT

A 66-year-old man of Lithuanian extraction (M.G.H. 789289) was admitted to the hospital on October 3, 1952, complaining of bloody diarrhea and a 15-pound weight loss of 6 months' duration. In the preceding 2 years he had suffered intermittently from constipation and had noted occasional bloody stools. He had otherwise enjoyed good health in the past.

Physical examination revealed no significant abnormalities other than moderate pulmonary emphysema and evidence of mild generalized arteriosclerosis with a blood pressure of 175/75. Rectal examination and proctoscopy disclosed a fungating, ulcerated tumor mass encircling the bowel lumen at a level 6 cm. from the anus. Biopsy of the lesion confirmed the presence of adenocarcinoma.

The results of laboratory studies, including blood counts, hemoglobin, urinalysis, nonprotein nitrogen, serum protein and electrolytes, were within normal limits. X-ray examination of the chest, an intravenous pyelogram, and an electrocardiogram showed no abnormalities.

The bowel having been prepared with Sulfathalidine started before admission, a combined abdominoperineal resection of the lesion was performed on October 6 under cyclopropane-curare anesthesia. The tumor was palpable just below the pelvic floor. There were enlarged lymph nodes along the superior hemorrhoidal artery, although none were palpable at the level of the aorta. Two tiny nodules only a few millimeters in diameter were felt high on the dome of the liver. These were not considered sufficiently conclusive of metastatic disease to justify a palliative resection of the primary growth. Accordingly, a radical colonic resection was carried out, with removal of all node-bearing tissue as high as the aortic origin of the inferior mesenteric artery, which was ligated flush with the aorta. The dissection was also extended laterally to accomplish a pelvic-lymph-node removal along the common iliac and hypogastric vessels. The colostomy was made in the middle third of the descending colon, preservation of the marginal artery having permitted a wide removal of mesentery proximally. At the conclusion of the abdominal operation the colostomy was perfectly normal in appearance, and there was no suggestion of impaired circulation in the remainder of the colon or small bowel, although no special note was made at the time of the character of the pulsations in the mesenteric vessels. The perineal portion of the procedure was performed in the standard manner.

Pathological examination revealed an adenocarcinoma, Grade 3, with extension to the serosal surface and metastases to 1 out of 11 mesenteric lymph nodes sectioned. In addition there were 2 adenomatous polyps in the sigmoid.

The patient seemed to convalesce uneventfully until the 3d postoperative day, when the clamp was removed from the colostomy and some necrosis at its tip was noted. He began to have liquid colostomy movements, and in the next 6 hours crampy abdominal pain, diffuse abdominal tenderness and an increasingly toxic appearance developed. It was suspected that gradual terminal gangrene of the colostomy had occurred, resulting in perforation and early peritonitis.

Re-exploration was therefore carried out on October 10, but an entirely different situation was encountered. There was a moderate degree of arterial insufficiency involving the entire large bowel and the small bowel from a few inches beyond the ligament of Treitz downward. There was a definite color difference between arteries and veins in the jejunum, but the venous blood was very dark and the bowel slightly cyanotic. In the ileum and the colon the arterial blood was dark, and in the cecum there were patchy areas of frank gangrene. Pulsations were neither visible in any of the smaller mesenteric vessels nor palpable in the superior mesenteric artery or its major branches. There were good pulsations in the celiac axis and in the common iliac arteries. It was believed that the only hope of salvage lay in exposure of the superior mesenteric artery and extraction of a possible thrombus or embolus from it. After proximal and distal control had been obtained, the artery was opened 5 to 7 cm. from its aortic origin. A very weak, pulsatile flow was noted proximally, and a fair, nonpulsatile flow from the distal arterial segment. A sucker tip was inserted through the proximal portion of the superior mesenteric artery into the aorta. No definite clot

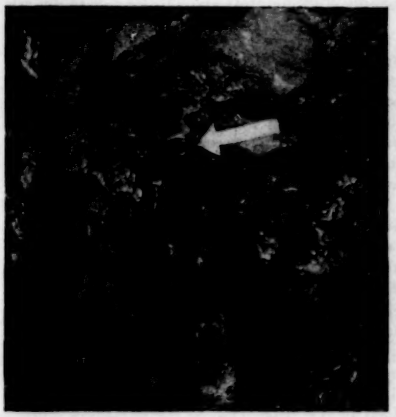

FIGURE 1. *Appearance of the Specimen at Autopsy. Multiple sections have been made through the superior mesenteric artery. The slit-like narrowing 1 cm. from the aortic orifice is indicated by the arrow. A portion of the arteriotomy suture line made at the time of re-exploration is visible in the lower part of the photograph.*

*From the Surgical Services, Massachusetts General Hospital, and the Department of Surgery, Harvard Medical School.

†Instructor in surgery, Harvard Medical School; assistant in surgery, Massachusetts General Hospital.

‡Assistant resident in surgery, Massachusetts General Hospital.

was evacuated, and only slight improvement in flow resulted from this maneuver. The arteriotomy was closed, and no further manipulation was attempted other than to infold the wall of the cecum containing the areas of frank gangrene.

Postoperatively the patient's condition continued to deteriorate, and death occurred 7 hours later.

Post-mortem examination was performed 9 hours later. The pertinent portions of the autopsy protocol* are summarized as follows:

With the exception of the first 70 cm. of small intestine distal to the ligament of Treitz, there was extensive infarction of the small and large intestine; the greater the distance from the celiac axis, the more extensive and advanced the process in the bowel. About the orifices of the celiac axis and the superior mesenteric artery there was marked atherosclerosis of the aorta, with intimal ulceration. The orifice of the celiac axis was widely patent, and the vessel itself was soft and widely patent throughout its major divisions and smaller branches. The first 3 cm. of the superior mesenteric artery contained a large, yellow, atheromatous plaque with calcification. The lumen at a point 1 cm. from the aortic orifice was narrowed to a slitlike opening barely admitting a fine probe (Fig. 1). No definite ante-mortem thrombus could be identified. Distal to this region the superior mesenteric artery and all its branches were soft and widely patent. The inferior mesenteric artery had previously been ligated by a silk suture and sectioned at its origin.

Unexpected findings were a single liver metastasis, 0.8 cm. in diameter, in the posterior right lobe, and a solitary pulmonary metastasis, 1 cm. in diameter, in the left upper lobe. The 2 small hepatic nodules palpated at operation proved to be hyalinized areas.

Discussion

It is believed that the patient had suffered gradual atheromatous occlusion of the superior mesenteric artery and had become dependent on collateral channels from the inferior mesenteric artery and celiac axis for circulation to the bowel. High ligation of the inferior mesenteric artery left only the collateral circulation from the coeliac axis, which, with the small residual flow through the markedly narrowed superior mesenteric artery, was sufficient to avert any immediate pronounced ischemia of the bowel below the ligament of Treitz. Either cumulative anoxia or subsequent thrombosis in a vascular bed rendered relatively stagnant by interruption of the inferior mesenteric collateral flow led to eventual massive infarction and ultimate death. In retrospect, it is believed that prompt endarterectomy of the proximal superior mesenteric artery, an instrument similar to the Potts clamp being employed for proximal aortic control, might have reversed the process. No previous report of a similar complication of inferior mesenteric-artery ligation could be found in the literature.

Gradual arteriosclerotic occlusion of the superior mesenteric artery with development of adequate collateral circulation to the bowel via the inferior mesenteric artery and celiac axis has been recognized in the past. Moore,[4] in a review of mesenteric vascular occlusion, cited the known reported cases in which this had occurred without organic bowel changes and with only occasional functional disturbance. He suggested that such a situation may exist without symptoms more frequently than is recognized. Furthermore, certain vascular anomalies known to occur occasionally in this region would also present circumstances wherein high ligation of the inferior mesenteric artery or its anatomic equivalent might have disastrous consequences. For example, Steward and Rankin,[5] in a study of the blood supply of the colon, reported a case in which the right colic and middle colic arterial distribution arose from the left colic branch of the inferior mesenteric artery, and another case in which a single main trunk gave origin to the various branches of both superior and inferior mesenteric-artery supply.

The above discussion is by no means intended to suggest that ligation of the inferior mesenteric artery at its aortic origin is sufficiently fraught with danger to preclude its routine use. Certainly, the reasons for the adoption of this maneuver in performance of adequate resections for carcinoma of the descending colon and rectum are clear cut and indisputable. Undoubtedly, this technical feature will find increasingly widespread use. It seems important, therefore, for surgeons to be aware of the possible existence of situations similar to the one reported above and alert to their recognition before sacrifice of the inferior mesenteric artery. In addition to preliminary search for abnormalities of the mesenteric vascular pattern, it is recommended that the inferior mesenteric artery be temporarily occluded while pulsations in the superior mesenteric artery and its major branches are sought. Should this maneuver suggest that the inferior mesenteric artery is serving as an important collateral channel or that a vascular anomaly exists, ligation would have to be performed at some more distal point.

*M. G. H. Autopsy No. 15798.

Summary

A case of massive mesenteric infarction after high ligation of the inferior mesenteric artery in resection of the rectum and sigmoid for carcinoma is reported. This complication is believed to have been due to a previously existing atheromatous occlusion of the superior mesenteric artery. Such a complication should not be allowed to occur when its possibility is recognized by the surgeon at the time of operation. An obvious means of avoiding the complication is suggested.

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ECTOPIC PREGNANCY OCCURRING IN THE RIGHT INGUINAL CANAL

ALEXANDER A. LEVI, M.D.*

BOSTON

THE purpose of this paper is to present a case of pregnancy occurring in the right inguinal canal, between the layers of the abdominal wall. A careful survey of the medical literature failed to reveal any similar case; the review included a number of the current textbooks on obstetrics and gynecology. Curtis[1] states that "The incidence of extrauterine gestation is estimated by Schumann as one in 300 pregnancies." He also lists 19 authors at the end of his chapter on ectopic pregnancy, none of whom describe a case similar to that reported below. Eastman,[2] in discussing a rare type of ectopic gestation, states that "Abdominal pregnancy occurs once in every 15,000 pregnancies approximately." He has listed at the end of his chapter on ectopic pregnancy 49 references to papers written on the same subject, none of which refer to a case of pregnancy occurring within the abdominal layers. Word[3] says that in his series of 140 cases, "The lesion was found 85 times in the right tube, 54 times in the left tube and once in the right ovary." (He mentions these locations only.) Novak[4] states that "tubal pregnancy is overwhelmingly the most common form of ectopic gestation." He likewise does not refer to the abdominal wall as a site for ectopic pregnancy.

CASE REPORT

Mrs. R. G. (A.H. 48721) a 32-year-old woman, was seen on March 4, 1952, during the course of an office examination, because of a mass in the right side of the abdomen. She stated that her last regular menstrual period had begun on January 17, and the next on February 28. At that time she was "10 days overdue," and from then on flowing occurred in varying amounts every day, including the day of examination. She said that she had been somewhat nauseated and had noticed some enlargement of her breasts. She also stated that a mass had begun to develop in the right lower portion of the abdomen about 2 weeks before examination and that it had increased in size so that she could palpate it. The mass was very tender on standing or when she wore an abdominal girdle.

The past history was uneventful except for tonsillectomy and adenoidectomy and an appendectomy performed in January, 1946, with plastic repair of both ovaries and round-ligament uterine suspension. A low forceps delivery had been performed on February 20, 1948, and on December 28, 1949, another pregnancy had culminated in a normal delivery.

Physical examination disclosed a woman who was in obvious distress. She walked bent over, almost unwilling to use her right leg, with her hands trying to hold up the right lower portion of the abdomen. In the standing position, a mass about two thirds the size of a hen's egg was seen protruding through the skin in the region of the right external inguinal ring. This mass could not be reduced with the patient standing or lying down and was in the location where one might expect an inguinal hernia to form. On vaginal examination the cervix was normal, as was the uterus. The right adnexa could not be definitely outlined because of acute tenderness along the right inguinal canal over the mass described above. It was believed that the patient had an ectopic pregnancy and that the mass as described had probably migrated into the abdominal wall, although at the time it was not clear why this should be so. The patient was admitted to the Allerton Hospital, Brookline, Massachusetts, for operation, with a diagnosis of "possible ectopic pregnancy."

At operation on March 5, performed under spinal anesthesia, a scar was noted low in the midline of the abdomen, the site of a previous operation. This was excised. The skin was then further incised upward so as to include the umbilicus, where an umbilical hernia was observed. The incision was carried through the abdominal wall. A hernial sac was present in the region of the umbilicus. This was incised, and its contents were reduced. The omentum was found to be adherent to the pelvic cavity and to the left tube and ovary. These adhesions were freed. The left tube and ovary were found adherent to each other and to the sigmoid; these adhesions were separated. A loop of small intestine forming a "knuckle" adherent to the right ovary was separated. The right ovary was adherent to the posterior aspect of the right broad ligament, almost in the region of the uterosacral ligaments. The fimbriated end of the right tube was found to be adherent to the right ovary. The remainder of the tube was followed in its course, and a small "knuckle" at its midportion was found lying next to the posterior aspect of the peritoneum at the point where the round ligament had been pulled through during the previous suspension operation. The "knuckle" of tube was thoroughly investigated and definitely was shown not to have passed through the peritoneum at this point.

A mass about the size of a peach, which pushed up through the skin at a point opposite to the external inguinal ring, was found to be located not within the abdominal cavity but between the right rectus muscle and fascia, within the right inguinal canal. The fascia was dissected free from the rectus muscle, beginning at the midline. The dissection was carried to the mass, which was lying within the inguinal canal. The mass appeared cystic and bluish. The dissection was continued, and during the course of it the "cyst wall" ruptured. Tissue resembling placenta protruded through its wall. This was immediately followed by the protrusion of a fetus about 2 cm. long. Dissection proceeded in such a manner as to free the entire mass (golf ball in size) from the anterior wall of the rectus muscle.† The excision was then carried behind the fascia, around the lateral border of the rectus muscle, to include the round ligament, to which it was attached. The lateral edge of peritoneum was incised, and dissection was carried down into the abdominal cavity, so as to include the "knuckle" of the right tube and part of the right round ligament. Dissection was then begun within the pelvic cavity. The right tube and ovary were freed from their adhesions to the posterior aspect of the right broad ligament. The cornual end of the right tube was clamped, cut and tied. A portion of the round ligament was treated in similar manner, and all these structures, including the products of pregnancy attached to the round ligament at its distal point near the pubis, were removed.

The patient made an uneventful recovery and was discharged from the hospital on the 6th postoperative day.

The pathological report and description of the tissues was as follows:

> The specimen consists of a markedly distorted tube firmly adherent to the adjacent ovary so that the tubal fimbriae are plastered over the ovary and fused to it (Fig. 1). The tube appears to have an over-all length of 12 cm. The two thirds proximal to the ovary, which is more normal then the remaining third, is 1.5 cm. in diameter and shows attached fragments of blood clot as well as adhesions to apparently surrounding structures. The remaining third is the seat of marked dilatation, 3 cm. in diameter, with a shaggy, irregular covering, which permits visualization of a large amount of red-blue blood clot. No intact serosa can be determined and it appears as though there must have been penetration of the tubal wall at this point. In

*Member, departments of Obstetrics and Gynecology, Tufts College Medical School; surgeon, Department of Gynecology, Boston Dispensary.

†Two other surgeons saw the mass immediately after its exposure from its original position.

the portion most removed from the ovary there is a small fetus, measuring 2 cm. from crown to rump, attached by a slender umbilical cord to a recognizable, immature placenta. The fetus and placenta appear to be well preserved, and the placenta is definitely attached to the tube although apparently extruded from it. Several fragments of apparent gray membrane, which may represent fascia, are attached to the tube.

Microscopical examination through the obvious placental tissue confirms the presence of immature chorionic villi covered by an abundant double layer of chorionic epithelium, with poorly developed vascularization of the stroma.

FIGURE 1. *Photograph of the Actual Specimen. The pregnancy sac and fetus are on the right, and the ovary at the left. The intervening tissues represent round ligament, peritoneum and muscle structures.*

This epithelium and stroma appear well preserved and there is no evidence of infarction, necrosis, intervillar thrombosis or inflammatory reaction. In the multiple sections taken through the tube a distinct decidual reaction is present within the subepithelial stromal cells, immediately under the lining epithelium. There are also placental giant cells in close approximation to the underlying smooth muscle (interpreted as indicating an original intratubal implantation of the gestation). In one cross section taken through the tube an area of striated muscle is present outside the tube in immediate association with some connective tissue that shows a striking decidual response; in the same area there are several suggestive giant cells, which may be of placental type. This approximation of decidual reaction, giant cells and striated muscles is distinctly suggestive of the possibility that the pregnancy occurred in some abnormal situation within or on the abdominal wall.

The diagnosis was rupture with ectopic pregnancy, presumably tubal in origin, with possible reimplantation in striated muscle.

Discussion

The position of the pregnancy, right tube and ovary is shown in Figure 2. The mechanism whereby

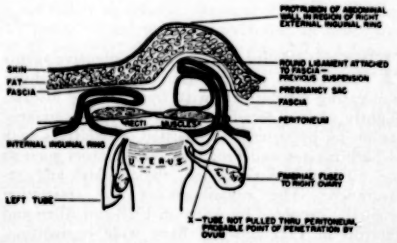

FIGURE 2. *Diagram, Showing the Location of the Pregnancy. The right tube was attached to the peritoneum at the internal inguinal ring.*

the pregnancy lodged in the inguinal canal is of interest. In my opinion the tube, which had attached itself to the peritoneum at the point through which the round ligament had been drawn during the previous suspension, was perforated by the conceptus, which migrated downward into the inguinal canal, where it became implanted and grew. Figure 2 clearly demonstrates this possibility.

Summary

A case that may be the first recorded instance of ectopic gestation within the abdominal wall is reported. It is suggested that the pregnancy in this unusual site occurred because of weakening of peritoneum by a previous surgical procedure, with migration of the fetus downward into the inguinal canal.

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MEDICAL PROGRESS

THE MEDICAL MANAGEMENT OF ARTERIAL HYPERTENSION*

EDWARD MEILMAN, M.D.†

BOSTON

THE availability of powerful hypotensive agents has placed new responsibilities on the physician caring for patients with hypertensive disease. Slightly over a decade ago the medical armamentarium for hypertension consisted of sedatives such as barbiturates and bromides, vasodilators such as the nitrites and xanthines, thiocyanates and reassurance.[1] The advantages of salt restriction originally proposed by Allen[2] in 1920 and Allen and Sherrill[3] in 1922 did not have wide recognition. In fact, diet was recommended only for obesity. The role and the effectiveness of psychotherapeutic measures were, however, well understood.[4, 5]

The large group of patients with "essential" hypertension were generally considered to have a hereditopsychogenic disorder. This point of view, having much to support it, resulted in the acceptance of hypertension and its sequelae as an inevitable process. It even fostered the obstructive point of view that lowering the blood pressure was to be avoided. The search for hypotensive drugs was little encouraged.

At present, physicians are beset by a growing volume of advertising, of clinical reports and of samples of powerfully hypotensive drugs. For many of these the advertisements precede the published articles that they selectively quote. The virtues of some products are extolled, and for others claims are suitably tempered with appropriate precautions. In view of the different mechanisms of action of these drugs and the multiplicity of side effects, full understanding of their physiologic and pharmacologic properties is necessary before they may be used safely.

SELECTION OF PATIENTS FOR TREATMENT

Before the hypotensive drugs available today are discussed separately and in detail, it is desirable to establish which patients with hypertension require treatment with these drugs. In this connection, earlier definitions of elevated blood pressure have recently been challenged by Masters et al.[6] In a study of 16,000 cases they determined that arterial blood pressure rises with increasing age so that for men, the "normal" pressure is 110–145 systolic, 68–92 diastolic, at age thirty, 110–155 systolic, 70–96 diastolic, at age forty-five and 115–170 systolic, 70–100 diastolic, at sixty. For women the values are somewhat lower before and a little higher after the menopause. If a level of 150 systolic, 100 diastolic, is arbitrarily set as the upper limit of normal, a third of the men and two fifths of the women (in 15,000 persons) over forty years of age have hypertension, and the majority of men over sixty and women over fifty have it. Such data can be interpreted in either of two ways: that blood pressure rises normally with advancing age; or that hypertensive disease has a higher incidence in older age groups. Regardless of interpretation, this information is of considerable interest when compared to levels of "normal" blood pressure, based on the highly selected data of insurance companies. Thus one can now give patients firmer assurance that their blood pressures are "normal for their age." Moreover, it is doubtful if at present patients with moderate elevations within the "normals" of Masters and his associates should receive treatment of any kind.‡

Certainly, many patients with considerable degrees of hypertension live close to their normal life expectancy.[7-9] Burgess[7] has shown that patients who have had known high blood pressures (at least 180 systolic, 100 diastolic) for eight years without evidence of cardiac, renal or severe fundal changes will live to within three or four years of their normal expectancy. Therapy should be reserved for patients with definite evidence that the heart, cerebrovascular system or kidneys are not tolerating the sustained level of hypertension or with severe symptoms from the hypertension. Three separate studies[10-12] have demonstrated the similarity of the cerebral and retinal arterioles in their reaction to nervous stimuli as well as pharmacodynamic agents. This suggests that the state of the cerebral vessels may be inferred by examination of the fundi.

Obviously, patients with malignant hypertension or with congestive heart failure due to hypertension should be treated vigorously. In addition, persons whose hypertension is of relatively short duration (under eight years) and who already show cardiac involvement such as enlargement, left-ventricle "strain" by electrocardiogram or angina pectoris, or severe changes in the optic fundi, such as hemorrhages or exudate, or albumin in the urine should be treated. Patients who show similar changes only after fifteen to twenty-five years of known hypertension should probably be treated less vigorously, since they have already demonstrated considerable

*From the Department of Medicine and the Yamins Research Building, Beth Israel Hospital, and the departments of Medicine and Pharmacology, Harvard Medical School.

†Instructor in medicine, Harvard Medical School; associate in medicine, Beth Israel Hospital.

‡With the future advent of safe and easily administered drugs with suitable properties, it may be desirable to treat even mild degrees of hypertension in the hope of preventing or delaying the cardiovascular and renal complications. But the hypothetical drugs for this (hypothetical) prophylaxis are not yet available.

resistance to the disease. Nevertheless, this group with long-standing hypertension, and beginning loss of adaptation to it, can be materially helped by successful hypotensive measures.

It is easier to be specific about which patients should not be treated with presently available drugs. Elderly persons, especially with a history of long-standing hypertension (fifteen years or more) and no evidence of hypertensive disease other than moderate enlargement of the left ventricle, are best left free of dietary and drug restrictions. Patients with high systolic pressures but diastolic levels of 100 of less, especially those over sixty years of age, usually require no hypotensive drugs. Persons in their twenties, with no symptoms or signs other than moderately elevated blood pressure, usually require only supportive psychotherapy to prevent development of a hypertension neurosis.

Aims of Treatment

Proof of the efficacy of drugs in lowering blood pressure in acute situations is at hand. Proof of their usefulness in long-term control of high blood pressure will require significant alteration in survival rates as has been shown for sympathectomy.[13-15]

In the absence of such studies one must rely on symptoms, which are notoriously difficult to evaluate,[16] or signs. The latter, heart size, electrocardiogram, appearance of optic fundi, kidney function and blood-pressure levels are much easier to evaluate since the careful study by Watkins et al.[17] on the salutary effects of hospitalization alone. The patient will be impressed by improvement in symptoms. The physician should find statistically significant alteration in blood pressure (measured under standard conditions, or at home) and then improvement in heart size, electrocardiogram, fundi and possibly even kidney function. The necessity for careful and critical analysis resides in the fact that most of the drugs to be discussed do not lower the blood pressure continuously; they produce intermittent lowering of the pressure not very different from the normal daily variation in many labile hypertensive patients.[4]

Salutary effects on the manifestations of hypertensive disease have generally followed successful reduction of blood pressure regardless of the drug or mechanism involved. Until specific etiologic treatment for various kinds of hypertension (such as surgery for pheochromocytoma or coarctation) is available, one will have to rely on hypotensive drugs and agents, choosing those which least disturb important homeostatic mechanisms. For each patient the theoretical advantages to be gained must be weighed against the restrictions, discomfort and dangers imposed by the therapeutic regimen.

Low-Sodium Diets

An effective measure in many cases of hypertension has been the dietary restriction of salt,[3, 18, 19] of which the rice, fruit and sugar diet is an extreme example. This diet, popularized by Kempner,[20-24] has the lowest content of sodium, cholesterol, protein and fat of almost any conceivable diet*[22] and its efficacy when applied as prescribed by Kempner[22] is significant. Approximately two thirds of 500 patients were benefited by the diet by one or more of the following criteria: decrease of at least 20 mm. in "mean" blood pressure, reduction in heart size by 18 per cent, change in T wave in Lead 1 from inverted to upright, and improvement or clearing of severe retinopathy. Twenty-five per cent of the patients obtained blood-pressure levels below 145 systolic, 95 diastolic. A carefully controlled study by Watkins et al.[25] of 50 patients who received the rice diet for a mean of ten and a half weeks has confirmed Kempner's claims for the beneficial effect on symptomatology, hypertension, retinopathy, electrocardiographic changes, cardiac enlargement, electrolyte and nitrogen metabolism and decrease in serum cholesterol. Watkins and his associates state that there can be "little doubt that the Kempner rice diet has an important place in the treatment of severe forms of hypertension."

During the initial month or two of the rice diet there is always a considerable loss in weight. A nitrogen loss amounting to about 2.5 per cent of the total nitrogen content of the body occurs, but thereafter nitrogen equilibrium is maintained.[26] During this time a low sodium syndrome developed in 4 of 80 patients without evidence of major renal disease.[27] The commonest complication noted by Watkins and his co-workers[25] was exacerbation of symptoms of peptic ulcer.

Under some circumstances the rice diet has been maintained for several years.[22] However, for most patients it is discouragingly monotonous and cannot be tolerated for long, so that it is in general an unsatisfactory means of control.[25, 28, 29] Its main value is in the treatment of malignant hypertension,[22, 24, 25] and its greater usefulness in inducing patients to accept a 200-mg., low-sodium diet with gratitude. That the effectiveness of the rice diet depends on its low content of sodium is now well recognized.[25, 29-31] Corcoran et al.[29] reported that a fourth of their patients with severe hypertension responded favorably to diets containing less than 0.5 gm. of sodium daily. Diets containing over 500 mg. of sodium had little hypotensive effect, and in most cases, an increase in the sodium content above such levels was accompanied by a rise in the blood pressure. Patients on low-sodium diets should have occasional analyses of twenty-four-hour urine for sodium (or chloride, if no salt substitute is used). This will reveal whether any hypotensive effects observed are paralleled by low-sodium intakes or result merely from the reassurance of a dietary program and the enthusiastic interest of the physician. Close watch is required, especially in the presence of renal disease, to detect low-sodium syndromes.

*The rice diet contains, per 2000 calories, 5 gm. of fat, 20 gm. of protein, not over 200 mg. of chloride and 150 mg. of sodium and no cholesterol.

Although Kempner claims that improvement may require as long as a year of sodium restriction, in most cases any blood-pressure response to be obtained is observed in two or three months. Even in cases in which sodium restriction itself has not been very effective, however, it must be considered as a useful adjunct to the other forms of therapy discussed below.

Cation-Exchange Resins

Various workers have attempted to ease the restrictions of a diet containing 200 to 500 mg. of sodium by allowing the patient more salt, which is then removed from the intestinal tract with cation-exchange resins.[30, 32, 33] Careful metabolic and clinical studies of the action of these resins in various edematous states have been made.[34-39] The cation-exchange resins all have certain features in common: they cannot remove sodium selectively; and they also remove potassium, calcium, magnesium and other cations such as alkaloidal drugs, streptomycin and amino acids. In exchange for the sodium or other cations removed the resins give up hydrogen or ammonium ions, which are then absorbed from the intestinal tract. Their efficiency varies. Permutit can remove 5 milliequiv. (115 mg.) of sodium per gram of resin.[40] Resodec, which contains an ammonium carboxylic and also a potassium carboxylic resin to prevent depletion of body potassium stores, will remove 23 to 46 mg. of sodium per gram of resin,[33] if the patient is on a 1-gm. sodium diet. Carboresin, which contains, in addition, some anion exchangers to reduce the tendency to acidosis, will remove 23 mg. of sodium per gram of resin, if the patient is on a 1.5-gm. sodium diet.[41] Unfortunately, efficiency in removing sodium is no guarantee of clinical usefulness. A dose of 100 gm. of Permutit, which can remove 11.5 gm. of sodium, will release for absorption by the gut 25.7 gm. of ammonium chloride (the chloride appearing from the gastric secretions).[40] Moreover, this resin removes calcium, potassium and magnesium even more efficiently than sodium.

The urine becomes quite acid, and urinary casts are common. Various degrees of metabolic acidosis, low-salt syndrome, hypopotassemia and hypocalcemia occur.[40] Electrolyte disturbances are almost inevitable in patients with renal insufficiency. The presence of acidosis may prevent symptoms of hypocalcemia, even though the serum level of calcium falls. Ingestion of 2 gm. of calcium lactate and 2 to 4 gm. of potassium citrate daily is recommended to prevent deficiencies of potassium and calcium, but this, of course, diminishes the efficiency of the resin.

None of the resins allow a normal diet. Salt restriction usually to 1 to 1.5 gm. of sodium daily[41, 42] is necessary to lower the urinary excretion of sodium to 0.5 gm. or less. In addition to the large bulk required (variously stated as 30 to 100 gm.[40] and 45 gm.[32]) and relative unpalatability, the resins may cause constipation, abdominal fullness, anorexia, nausea and vomiting. The stools become hard and gritty, and in elderly patients fecal impaction may occur. However, in patients whose blood pressure responds to sodium restriction, the use of these exchange resins may offer a greater latitude in diet, sufficient to make up for the discomforts and metabolic disturbances from the resin. Close observation of the patient and occasional determinations of blood carbon dioxide, chloride and nonprotein nitrogen, as well as twenty-four-hour urinary sodium excretions, are necessary for the safe and effective use of these agents.

Hypotensive Drugs

The need for a suitable oral preparation for the control of elevated blood pressure has led to a revival of interest in old drugs as well as attempts to synthesize new ones. Some of these stimulate the afferent end of reflex vasodepressor mechanisms (the veratrum esters); some inhibit sympathetic activity in the central nervous system (dihydrogenated ergot alkaloids); some act in the central nervous system and also peripherally (hydrazino-phthalazine); some work entirely on the efferent pathways by paralyzing ganglionic transmission (hexamethonium) or act directly on the smooth muscle of the arteriole (Dibenamine compounds) to prevent sympathetic vasoconstriction; some act on sodium metabolism in some poorly understood manner (thiocyanates); and the hypotensive action of some is scarcely understood at all (*Rauwolfia serpentina*, pyrogens).

Veratrum Alkaloids

The hypotensive alkaloidal esters obtained from the roots of veratrum plants include protoveratrine,[43] germitrine, germidine[44] and neogermitrine.[45] A biologically standardized extract containing a mixture of esters from *Veratrum viride* (Veriloid) has been studied extensively.[46-52] The only one of the pure esters that has received clinical investigation thus far is protoveratrine* from *Veratrum album*.[54-62]

These substances exert their hypotensive action in a unique manner, being the only known clinical agents that can stimulate the afferent side of the reflex pathway[63-66] presumably responsible for the normal control of blood pressure. Afferent nerve endings, predominantly in the left ventricle,[67] but also to some extent in the carotid sinus, aortic arch and pulmonary arteries,[68, 69] are "sensitized" so that they send increased afferent stimuli up the vagus[70, 71] to the vasomotor center causing a reflex (neurogenic) fall in blood pressure and heart rate. The veratrum alkaloids also block the carotid-sinus pressor reflex,[66] and this property is the basis of a new bioassay method.[72] There is evidence

*Protoveratrine has now been separated by counter-current distribution into two substances, protoveratrine A and protoveratrine B, which differ by one oxygen. Their biologic activity is similar, protoveratrine A being indistinguishable from protoveratrine. The material used by Meilman and Krayer[54, 55] contained 40 to 50 per cent protoveratrine B.

for a direct action of the veratrum esters on the central nervous system,[70, 74] but the major effect is probably reflex. The nature of the efferent pathway that causes dilatation of the arterioles is not yet clear; the efferent path in the vagus results in the characteristic bradycardia. Atropine readily antagonizes the bradycardia without, as a rule, affecting the hypotension.[48, 54, 75]

The hypotensive veratrum alkaloids cause no paralysis of sympathetic activity.[46] The cold-pressor reaction still occurs,[54] although it is usually diminished. There is no postural hypotension, except briefly at peak action of the drug.[54] The hypotension is easily counteracted by sympathomimetic amines such as ephedrine. Protoveratrine and mixtures of veratrum esters (Veriloid and Veratrone) have been shown to cause a moderate peripheral vasodilatation with a decrease in cerebrovascular resistance[76] and in renal resistance.[59] In fact, renal vasodilatation during periods of lowered blood pressure from protoveratrine occurs in patients with chronic nephritis as well as those with essential hypertension. Unlike the "renal hyperemia" from pyrogens,[77] the renal vasodilatation from protoveratrine occurs without rise in cardiac output.[57]

The main advantage of crystalline alkaloids such as protoveratrine over alkaloidal mixtures appears to be that dosage can be based on weight, rather than bioassay,[78] a matter of importance since the therapeutic range is relatively narrow. The dose-response relations of protoveratrine by different routes of administration have been established, and the drug can be given with predictable and reproducible results.[46]

Administered parenterally, protoveratrine is very effective in lowering the blood pressure in a variety of hypertensive states, including essential hypertension, acute and chronic renal disease, malignant hypertension, carcinoma of the adrenal cortex, toxemia of pregnancy and ACTH or cortisone toxicity.[55] Protoveratrine and *Veratrum viride* mixtures are virtually specific for the control of hypertensive encephalopathy and the convulsions of eclampsia.[53, 55, 60, 79-84] In a child with acute glomerulonephritis complicated by severe hypertension and congestive heart failure, protoveratrine proved life saving when digitalis and magnesium sulfate had been ineffective.[55] It may be a useful aid in some cases of hypertensive pulmonary edema.[56] I have seen gross papilledema clear completely in two weeks with two daily injections of protoveratrine. The usefulness of protoveratrine for acute hypertensive situations seems clear.

The management of severe hypertensive disease by repeated subcutaneous or intramuscular injections two or three times daily is burdensome, but Currens[61] has followed 2 patients who administered protoveratrine to themselves for seven months. No tolerance appeared, and the dose remained relatively constant.

The intravenous dosage of protoveratrine is 1.5 to 1.9 microgm. per kilogram, with subsequent doses of 20 microgm. at ten-minute intervals until a satisfactory hypotensive effect is obtained. Continuous intravenous infusion at rates of about 1 microgm. per minute maintained the lowered blood pressure at a steady level as long as the infusion was continued (in 1 case for four days). Subcutaneous or intramuscular doses of protoveratrine require 4 to 6 microgm. per kilogram at intervals of eight to twelve hours.[56]

Oral administration of protoveratrine as well as crude veratrum alkaloids can cause significant lowering of blood pressure in some hypertensive persons, regardless of the etiology of the hypertension, with rare toxic reactions.[52, 56, 61, 62] However, in some patients, the pure as well as the crude alkaloids, taken by mouth, cause lowering of blood pressure only with doses that induce nausea and vomiting. In some, nausea and vomiting may occur without a fall in blood pressure. However, in patients who responded favorably to oral administration of protoveratrine (a third of those who responded to parenteral administration), significant lowering of blood pressure during part of each day could be achieved for many months.[56] Concomitantly, many hypertensive symptoms, such as headache, tenseness and palpitations, were relieved. I have observed 2 patients on protoveratrine given by mouth for over a year who have had reversal of inverted T waves in Leads V_4, V_5 and V_6 of the electrocardiogram. The oral dose is 0.5 to 0.75 mg. three or occasionally four times daily after meals and at bedtime. Protoveratrine has been given in this fashion for over two years without any toxic effects other than an occasional episode of vomiting or a rare, severe hypotensive reaction and without development of tolerance. Hoobler et al.[62] suggested that protoveratrine be given in one large dose after breakfast (0.5 to 1.5 mg.), followed by one to two small doses (0.25 mg.) at intervals of two or three hours. A fall in blood pressure lasting six to eight hours during the most active period of the day was obtained in 70 per cent of patients. This intermittent lowering of blood pressure has caused marked amelioration of severe hypertensive symptoms, such as congestive heart failure and improved vision in malignant hypertension and has relieved encephalopathy. For patients with nocturnal dyspnea, Hoobler and his associates suggested a similar dosage schedule starting after supper. They stated that the drug administered as described by them was superior to Veriloid and had a smaller incidence of vomiting. It was emphasized that the drug was palliative rather than curative.

The failure of some authors[50] to obtain significant blood-pressure changes with veratrum alkaloids given by mouth is due to the fact that only a minority of patients respond favorably, and in

those who do, hypotensive effects occur intermittently.[56, 82] Others report that a fifth[81] or a quarter[82] of their patients showed a significant fall in blood pressure. With critical attention to dosage[56, 82, 87] Veriloid and protoveratrine have caused significant reduction in blood pressure with only occasional toxic reactions in about a third of patients.

Overdosage with veratrum alkaloids causes severe though transient toxic effects, which may occur with any route of administration. These begin with substernal and epigastric oppression and may progress to severe nausea and vomiting. At such times hypotension and bradycardia are usually quite marked, the patients sweat profusely, and body temperature falls. The hypotension and bradycardia may be overcome by ephedrine sulfate (25 to 35 mg. subcutaneously) and atropine (0.5 to 1.0 mg. intravenously or intramuscularly). The patient should be cautioned to lie flat during such an episode. Vomiting will cease spontaneously in thirty minutes to an hour, but it may be moderated by subcutaneous or intravenous administration of barbiturates such as Amytal and phenobarbital. The patient should be forewarned about the possibility of toxic reactions; the physician must not be led into the mistaken diagnosis of myocardial infarction because of the concomitance of epigastric oppression, sweating and hypotension. An electrocardiogram taken during such an episode may show inverted T waves,[88] sharply localized to Leads V_5 and V_6, which are due to intense vagal stimulation. Protoveratrine has been given intravenously to hypertensive patients with angina pectoris in a dosage sufficient to cause marked hypotension without inducing chest pain or electrocardiographic evidence of ischemia.[89] It has been suggested that the veratrum alkaloids are more effective with a low-sodium diet[48] and, more recently, in conjunction with the drugs mentioned below.

Rauwolfia Serpentina

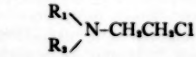
Rivaling the new synthetic hypotensive drugs in interest is a very old Indian drug, derived from folklore. It was formerly used in a variety of situations, including insanity, presumably for its sedative effects.[90] More recently, its moderate hypotensive action and relative freedom from side effects have been described.[91-93] Vakil,[92] using placebo controls, showed that 44 per cent of 50 patients had a fall of 20 systolic and 10 or more diastolic and that the hypotensive action was still evident in most of these four weeks after the drug had been discontinued. Wilkins and Judson[94] have introduced the drug into the treatment of hypertension in this country and have confirmed the observations of the Indian workers. The drug was found to be well tolerated for long periods, the only side effect of note being a strong sedative action.[94] Diarrhea has been reported after excessive doses.[95] Gujral[96] observed a patient who took a large overdose and suffered no ill effect although his blood pressure remained at 86 systolic for two weeks. The hypotension can be overcome by ephedrine or phenylephrine. Bradycardia characteristically occurs and is blocked by atropine.[95] Nasal stuffiness is common, and this, together with the bradycardia, has suggested that the drug has a central "sympatholytic" action. However, there is neither postural hypotension nor ganglionic blockade. Actually, the mechanism of action is poorly understood. The reason for the gain in weight that many patients experience is equally obscure.[94] Tolerance to the drug apparently does not develop[94, 95] even when it is given continuously.

Rauwolfia serpentina appears to be a drug of moderate hypotensive activity, more useful by itself in milder cases of hypertension, particularly young persons with labile blood pressures.[94] Disappearance or diminution of the emotional pressor responses, tachycardia and "diencephalic" flushing characteristic of some of these patients has been observed.[96]

Wilkins[97] has pointed out the "striking additive if not synergistic" effects of *Rauwolfia serpentina* with veratrum and hydrazinophthalazines (described below) in severer forms of hypertensive cardiovascular disease. Further work on this remarkably nontoxic agent will be awaited with interest.

Dibenamine Compounds (SKF-688A)

At present only pheochromocytoma and intracranial lesions are causes of hypertension in human beings that definitely involve overactivity of the sympathoadrenal system. The role of increased sympathetic activity in essential hypertension is still obscure.[98] Nonetheless, adrenergic blockade is effective in lowering blood pressure in a considerable number of patients with essential and malignant hypertension.[98-102] The most active compounds are the β-halo-alkylamines, whose general formula is as follows:



These agents combine irreversibly with the effector organ (for example, the smooth muscle of arterioles) and prevent it from responding normally to adrenergic mediators.[103] Thus, epinephrine, which normally causes a rise in blood pressure, after Dibenamine will cause no rise or even a fall in pressure (epinephrine reversal). The characteristic tachycardia from epinephrine is not inhibited; in fact, it may be exaggerated,[104] because there is no rise in blood pressure and consequent reflex cardiac slowing.

Dibenamine must be given by slow intravenous infusion and must be diluted.[91] A dose of 5 mg. per kilogram of body weight usually causes a marked orthostatic hypotension that may last as long as five or six days.[101] The fall in supine blood pressure, if any, may last a few to over twenty-four hours. The pupils become constricted, and the nose is congested. The skin temperature of the extremities rises.[100] The patient is generally aware of heart action because of the peripheral vasodilatation and increased stroke volume.[104] Besides the disadvantage of intravenous administration, Dibenamine has occasionally had marked excitatory effects on the central nervous system (confusion, restlessness or, rarely, transient psychosis), as well as drowsiness, nausea and vomiting.

In 7 of 10 patients with malignant hypertension,[99] temporary improvement in hypertensive encephalopathy was induced with intravenous administration of Dibenamine, suggesting its use as an accessory measure to tide patients over an acute episode. However, the drug is certainly not the agent of first choice in such situations. Its effects last for days and cannot be overcome even with large doses of pharmacologic agents such as epinephrine (that is, it is not a competitive inhibition).

An orally effective Dibenamine congener (SKF-688A, n-phenoxy-isopropyl-N-benzyl-β-chloroethylamine hydrochloride, Dibenzyline) has recently been synthesized, and a few studies have appeared concerning its use.[100, 102, 104] Three daily doses, given with meals to patients with benign or malignant hypertension, caused a moderate fall in supine and a marked fall in orthostatic blood pressure. Improvements in electrocardiogram and fundi were seen in 2 patients. Hypertensive symptoms were relieved. Tolerance appeared not infrequently, and doses had to be increased to obtain continued responses. Hence, the daily dose varied from 30 to 560 mg. Side effects (actually evidence of adrenergic blockade) included marked miosis (resistant to Neo-Synephrine), dryness of the mouth, nasal congestion, drowsiness, fatigue, inability to concentrate and, rarely, nausea and vomiting. In normal dogs 688A caused a fall in blood pressure, accompanied by a slight increase in renal blood flow.[105]

Of 32 patients who received 688A for three to six months, angina pectoris during postural tachycardia developed in 3, and congestive failure in 1.[106] Symptomatic improvement was noted in 16 of 22 patients who received 688A.[101] In these there was partial inhibition of the cold-pressor test. In a study of 11 patients[102] who received the drug for months the effects on supine and postural blood pressure, as well as the cold-pressor reaction, compared so favorably to that of sympathectomy that the authors suggested the value of a long-time clinical trial in an effort to duplicate the salutary effects of sympathectomy on survival rates.[15] SKF-688A is of much shorter action than Dibenamine, all effects from a single oral dose usually passing off in three to five hours.[100] However, the prominence of postural hypotension, the inability to treat a severe hypotensive reaction except by raising the legs, and the apparently adverse effects on some patients with heart disease are significant disadvantages.

Dihydrogenated Ergot Alkaloids

In 1943 Stoll and Hofmann[107] hydrogenated four recently isolated ergot alkaloids and produced a new series of compounds, dihydroergotamine, dihydroergocornine, dihydroergocristine and dihydroergokryptine, all of which had considerable sympatholytic activity, with little or no vasoconstrictor action prominent with other ergot alkaloids.[108] Studies by Bluntschli[109, 110] Rothlin[108] and Freis et al.[111, 112] demonstrated that the sympatholytic action was central rather than peripheral.

When one of these drugs, dihydroergocornine (DHO), was given intravenously or intramuscularly in doses of 0.2 to 1.0 mg., normal as well as hypertensive patients had a fall in supine blood pressure of variable degree. Orthostatic hypotension or even collapse occurred without compensatory tachycardia. Bradycardia occurred characteristically and was adduced as evidence of depressant action on the vasomotor center; it could be overcome to some extent by atropine. Nasal stuffiness, fatigue, listlessness, nausea and vomiting were common. DHO inhibited vasoconstriction in the extremities and depressed vasopressor responses mediated over sympathetic pathways[111] such as the Valsalva overshoot and cold-pressor response. There was no change in cardiac output.[111] Total peripheral resistance diminished but not with any uniform pattern. Hepatic and renal blood flow decreased, whereas muscle flow increased,[111] as did renal vascular resistance.[113] Cerebrovascular resistance in hypertensive[114] but not in normal[115] subjects was diminished by DHO. Recovery to normal values of blood pressure required one to twenty-four hours. An interesting effect (from Hydergine*) is the increase in the renal extraction of para-amino hippurate,[116] particularly in patients in whom it is low, owing to either an intrarenal redistribution of blood or improved tubular function.

DHO caused no electrocardiographic changes when administered intravenously to 24 hypertensive patients, 6 with angina pectoris,[117] in contrast to the T-wave changes that occur after ergotamine or dihydroergotamine.

On oral administration the doses had to be increased to 4 to 10 mg., and hypotensive action was quite erratic[111] or absent.[118] Undesirable features were the development of vomiting (25 per

*Hydergine contains a mixture of dihydroergocornine, dihydroergokryptine and dihydroergocristine.

cent) even without much hypotensive action, oral ineffectiveness and marked postural hypotension. Of 17 patients who received Hydergine parenterally and orally for three to six months, 12 showed significant falls in blood pressure, and in 1 case papilledema cleared in fourteen weeks.[119]

Pyrogens

In view of the poor prognosis attending a diagnosis of malignant hypertension,[120] the vigorous treatment with pyrogens advocated by Page and Taylor[121] and Page [122] bears some comment. Renal insufficiency appears to be the only contraindication to treatment. The program entails endurance of a rigor and fever daily for six days each week, until the disease shows evidence of abating, which usually takes three or four months although occasionally as little as four weeks. Sodium must also be restricted. Of 20 patients, 5 refused to continue treatment. Of the remainder, 14 were followed; 9 were alive after fifteen to forty-five months, and 5 died of cerebral hemorrhages nine to thirty-seven months after treatment.

Such results justify even the most uncomfortable modes of treatment. However, this therapy is difficult to administer for several reasons: the dose of pyrogen (Pyromen) must often be rapidly increased to cope with developing tolerance of the patient to it; close attention is required to prevent and treat severe hypotensive reactions; and the patient must have a strong emotional make-up to endure the repeated pyrogenic reactions. The hypotensive drugs available today, as well as the low-sodium diet[22, 24, 25, 120] and sympathectomy,[15, 120, 123] offer better methods of dealing with malignant hypertension.

(To be concluded)

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MEDICAL INTELLIGENCE

"TOUCHING A CURE OF AN INVETERATE PHRENSY BY THE TRANSFUSION OF BLOOD"

CAPTAIN RALPH J. WEDGWOOD, M.C.,* AND GRETCHEN R. RIESE, M.S.†

SAMUEL PEPYS[1] referred as follows to the work of Drs. Richard Lower and Edmund King, which was presented at Gresham College, where the first attempts at transfusion were performed, and which led to a plot of intrigue, blackmail and possibly murder during this early phase of scientific progress, culminating in the obstruction of further investigation (in this case probably most justifiably) by governmental intervention:

> November 14, 1666: Tonight there was a pretty experiment of the blood of one dog let out till he died into the body of another on one side. This did give occasion to many pretty wishes, as of the blood of a Quaker to be let into an Archbishop, and such like: but may, if it takes, be of mighty use to man's health, for the mending of bad blood by borrowing from a better body.

Although Dr. Christopher Wren discovered the method,[2] the Honorable Robert Boyle[3] asserted that the transfusion of blood was first practiced on animals by Dr. Lower (in February, 1665) and proposed that "these trials be prosecuted to the utmost variety the subject will bear: as by exchanging the blood of old and young, sick and healthy, hot and cold, fierce and fearful, tame and wild, and that not only of the same but of different kinds." He added "It seems not irrational to guess aforehand that the exchange of blood will not alter the nature or disposition of the animals upon which it shall be practiced, though it may be thought worthwhile to determine that point by experiments."

Indeed, Drs. Lower and King did prosecute the experiment, and throughout Europe the natural philosophers "introduced into the veins" of animals a remarkable series of substances, including Aquafortis and Spirits of Vitriol.[4] Six months after Pepys' notation, on June 15, 1667, M. J. B. Denis took courage and transfused the blood of a lamb into a youth.[5] The news arrived in England, and by November 21 of the same year Pepys[1] describes the Royal Society as having found a suitable subject: "a man that is a little frantic that hath been a kind of minister, a poor and debauched man the college have hired for 20s. to have some blood of a sheep let into his body, and it is to be done Saturday next."

On that Saturday, November 23, 1667, "upon one Arthur Coga, at Arundel House, in the presence of many considerable and intelligent persons" the experiment was performed; the sheep was prepared, a cannula placed in the vessels and 9 or 10 ounces of the arterial blood of the living sheep conveyed into the veins of the subject. "The man after this operation found himself very well and has given his own narrative, enlarging more upon the benefit he thinks he has received by it than we think to own, as yet,"[6] and a week later Pepys[1] stated that "he speaks very well, and did this day (November 30th, 1667) give the society a relation thereof in Latin, saying that he finds himself much better since and as a new man; but he is cracked a little in his head, although he speaks very reasonably and very well."

On December 19, 1667, Denis, in Paris, performed a further transfusion, which tangled him in a net of intrigue, blackmail and bureaucracy. He wrote (to Mr. Oldenburg in London)[7]:

> You have doubtless heard of a madman that has been lately cured and restored to his understanding by means of a transfusion. The patient is about 34 years of age. His phrensy, occasioned by a disgrace in some amours, first was very violent and lasted ten months without any lucid interval; but returning afterwards by degrees to his wits he was married to a young gentlewoman, who was persuaded that his madness was a relick of a sickness and that there was no appearance he would ever relapse into it. This was far from proving so, he relapsed and has been several times restored within these seven or eight years. His last relapse was about four months since, and his wife shut him up and was even constrained to tie him because he was in such an extraordinary rage as to beat her. But he got loose, stark naked and ran away to Paris. He spent three or four months without sleep and his greatest diversion was to tear clothes that were given him, to run naked abroad, and to burn in the houses where he was whatever he could meet with. December 19 we used what art we could to dispose the fancy of our patient to suffer the transfusion, which we resolved should be tried upon him that night. Many persons of quality were present, together with several physicians and sur-

*Station surgeon, Quartermaster Climatic Research Laboratory, Lawrence, Massachusetts.
†Librarian, Quartermaster Climatic Research Laboratory, Lawrence, Massachusetts.

geons too intelligent to suspect them of being capable of the least surprise. M. Emmerez opened the crural artery of a calf (the blood of a calf by its mildness might allay the heat and ebulition of his blood) and did all the necessary preparations. We could give him no more than about five or six ounces by reason that his constrained posture and the crowd of spectators interrupted this operation. Meantime, he found himself very hot along his arms and under his armpits, and perceiving that he was falling into a swoon we stopped the blood running in and closed up the wound. He had supper two hours after, and not withstanding some dullness and sleepiness, passed that night with singing, whistling and other extravagancies.

The next morning we found him somewhat less extravagant, which induced us to believe that by repeating the transfusion once or twice we might find a more remarkable change. We therefore prepared ourselves to repeat it, and made this second transfusion more plentiful than the first. The patient must have received more than one whole pound. As this second transfusion was larger, so were the effects of it quicker and more considerable. As soon as the blood began to enter his veins he felt the heat along his arm and under his armpits he had felt before, his pulse rose, and soon we observed a plentiful sweat over all his face. His pulse varied extremely at this instant, and he complained of great pains in his kidneys, and that he was not well in his stomach, and that he was ready to choke unless they gave him his liberty.

While we were closing the wound he vomited, found himself urged to urine and asked to go to stool. He was made to lie down and after two hours straining to void diverse liquors which disturbed his stomach he fell asleep and slept until next morning. When he awoke he showed a surprising calmness and great presence of mind in expressing all the pains and general lassitude he felt in all his limbs. He made a great glass full of urine as black as if it had been mixed with soot. He remained sleepy all the rest of that day and went on to sleep well also the whole night following. Friday morning he filled another urinal almost as black as the day before, he bled at the nose very plentifully and, therefore, we thought it proper to take two or three small porringers of blood from him.

Saturday morning, the last day before Christmas, his urine cleared up and after that time it resumed its natural color. His wife confirmed the good effects of the transfusion assuring that instead of the kindness he now showed to her he used to do nothing but swear and beat her. I have seen him almost every day since. He is at present of a very calm spirit, performs all his functions very well, and sleeps all night long without interruption, though he says he now and then has troublesome dreams.

Shortly thereafter Oldenburg received an inquiry from Denis[8] whether the magistrates of London "had concerned themselves to prohibit the practice of transfusion of blood." His difficulties were more clearly defined in this communication of May 16, 1668. The wife of Denis' "madman" had requested that a further transfusion be given to her husband. Her motives may not have been entirely pure, for there is the suggestion that she was attempting to poison her husband and to make his death appear to be due to the transfusion:

> [She urged Denis] beyond measure, threatened that she would present a petition to the Solicitor General to enjoin us to do what we absolutely refused. Then she fell down with tears in her eyes and by unwearied clamor engaged us not to go away without having tried all possible means to recover her husband. Her art was great enough to make us condescend to another trial.

This third transfusion was never completed. "On opening the vein of the patient a violent fit seized him; there issued no blood out of the foot or the arm which obliged M. Emmerez to take the pipe into the arm without opening the artery of the calf, so without any transfusion. This poor man dying the night after."

Denis seems at this point to have become suspicious. "The next morning remembering the complaints the dead man had often made of his wife's attempts to poison him, we would gladly have opened his body, but she so violently opposed it that it was not possible. The wife had a hurried burial of her husband."

Shortly thereafter rumors, books and pamphlets circulated "false reports to decry this experiment." The wife, possibly not content with the convenient death of her husband, returned to Denis:

> [She] told us that some physicians did solicit her against us and that she had always refused them, knowing her obligations to us for having relieved her husband freely. Drawing hence no profit, as she expected she would, she turned her notices into menaces and sent word that in the present necessity to which she was reduced she was obliged to accept the offer made her by certain physicians if we would not assist her.

Denis "cared not for her threats," and the matter was brought before the courts. An English witness[9] described the social success of the trial as follows:

> . . . what M. Denis' advocate gloried in was that the experiment had been practiced with good, at least no ill, success in England, Germany, Italy, Holland, etc., and defended in these and almost all the universities of France. There were two persons present who had received a benefit and admiration of the experiment after they had been abandoned by physicians, that the most precious life to the state, his most christian Majesty, had been recently saved by a lately invented emetic.

Nevertheless, in spite of the odds on the defendant's side "his Majesty's attorney, because he thought there might be danger in permitting indifferently the practice of transfusion ordered that for the future no transfusion should be made upon any human body but by the approbation of the Physicians of the Parisian Faculty."[9]

The conflict was not only medical but also philosophic, for in spite of the logic expressed by Boyle, does not the blood contain the essence of character? Is it not the bearer of inherited traits? Cannot the person with the blood of a calf in his veins engender a calf for a child?

Six years later, in 1675, a papal bull banned the procedure, and one hundred and fifty years passed before the concept of "mending of bad blood by borrowing from a better body"[1] was raised and tested again.

The quotations used throughout this paper have been edited, spelling changed to modern usage, and extraneous words, sentences and paragraphs removed for the sake of brevity and clarity, it is hoped without altering their meaning.

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INFLUENZA A′ IN EARLY PREGNANCY

A RELATIVELY sharp outbreak of influenza A′ in Northern Ireland in December, 1951, afforded an opportunity for Campbell* to investigate its impact on the unborn babies of women pregnant at the time. For the purposes of survey influenza was defined as "a febrile illness with a sharp onset characterized by pains in the legs, back or head and sufficiently severe to require that the patient went to bed the first day of the illness falling between December 15 and January 21 inclusive."

On completion of the pregnancy and examination of the baby Campbell assembled information on whether the child was liveborn or stillborn and normal or deformed. Of a total of 116 infants whose mothers had contracted infection in the first trimester 3 were grossly defective (clubfoot, hydrocephalus and agenesis of kidney) and 3 were stillborn. Of 825 infants born at term after pregnancies that had not been complicated by influenza A′, 4 were grossly defective (clubfoot in 2 cases, ventral hernia in 1 and cardiac septal defect in 1), and 12 were stillborn. Campbell concluded that these findings did not suggest that influenza in the early months of pregnancy adds appreciably to the risk of stillbirth or fetal abnormality. Although this cautious — perhaps too cautious — conclusion may seem justified on the basis of the small numbers involved, further testing of influenza infections as a possible teratogen seems warranted. In the first place the rate of defect (assuming that a rate can be calculated on the basis of 3 cases) is six times as high in babies whose mothers had manifestations of infection in the first trimester as in those whose mothers did not. Secondly, it seems highly doubtful that all these babies were screened for lesser defects, such as cataracts and impaired hearing, that have established rubella so firmly as a teratogenic agent. Many of the lesser anomalies are not evident at a cursory inspection, and the figures given are not wholly satisfactory in exoneration of influenza A′. Further work remains to be done, and a step in this direction may be taken by physicians practicing obstetrics who answer the questionnaire reproduced below.

For the purposes of this inquiry influenza may be defined as an acute nonpyogenic respiratory infection (diagnosed as "cold," "grippe" or "flu" at the time) that caused the patient to go to bed for two days or more during the first four months of a pregnancy whose outcome is still not known. Such illnesses are limited to those occurring in January, February and March, 1953. If the physicians who took care of pregnant women who probably had influenza A′ as defined† would now provide the *Journal* with the information about the mother contained in the questionnaire, a satisfactory prospective study could be instituted and followed through to term as was done in the inquiry on rubella. Evaluation of the risks for the developing fetus of maternal influenza during the first two trimesters should be possible without bias (for results of the infection on the baby are as yet unknown). The following questionnaire lists the information needed for all cases of which there is knowledge:

(1) Physician's name and address
(2) Mother's name or initials
(3) Mother's age
(4) Date of last menstrual period
(5) Date of onset of influenza

After termination of pregnancy information about the baby (and the delivery of the obstetrician's next patient as a control) will be sought:

(1) Birth date of baby
(2) Stillbirth
  (a) Normal
  (b) Defective
(3) Normal
(4) Defective
  (a) Primary defect
  (b) Associated defect

*Campbell, W. A. B. Influenza in early pregnancy: effects on foetus. *Lancet* 1:173, 1953.

†The diagnosis should rest on an antibody rise in the second of paired serum specimens — a criterion that is impracticable for the present study.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39211

PRESENTATION OF CASE

A sixty-year-old man was referred to the hospital because of abdominal distention, obstipation and abdominal cramps.

For "many years" the patient had had frequent episodes of diarrhea and abdominal cramps during which the abdomen became distended and the cramps increased, with definite borborygmi. His weight increased or decreased depending on the frequency or duration of the attacks. Although he had been seen by a number of physicians in the past, a definite diagnosis was never established. The symptoms changed very little until four weeks before admission, when the abdominal distention and cramps became very severe, and although they were relieved from time to time by bowel movements they soon recurred. Since eating had made symptoms worse during previous episodes the patient had gradually taken less and less food. Because symptoms persisted he was admitted to another hospital, where a barium-enema examination was said to have revealed a cecosigmoid fistula. His bowels had not moved for several days before entry. He denied vomiting, chills, fever, melena or rectal bleeding. He had lost an estimated 15 pounds of weight during the past four weeks. He had had no previous operations.

Physical examination revealed a malnourished man, whose skin and tongue were dry. There was a Grade 1 apical systolic murmur. The abdomen was distended with a 15 cm., smooth, somewhat movable mass in the right lower quadrant extending into the right upper quadrant. It felt cystic and was tender. Bowel sounds were hyperactive but were of normal pitch. There was rebound tenderness over the right upper quadrant and the mass.

The temperature was 97°F., the pulse 95, and the respirations 22. The blood pressure was 102 systolic, 70 diastolic.

A urine specimen was normal. Examination of the blood revealed a hemoglobin of 12.8 gm. per 100 cc. and a white-cell count of 13,200, with 83 per cent neutrophils, 7 per cent lymphocytes, 8 per cent monocytes and 2 per cent phagocytes with ingested red blood cells. The prothrombin time was 14 seconds (normal, 14 seconds). The sodium was 124 milliequiv., the chloride 99 milliequiv., the potassium 4.9 milliequiv., and the carbon dioxide 21 milliequiv. per liter; the nonprotein nitrogen was 25 mg., and the total protein 4.0 gm. per 100 cc. A stool specimen was light brown and guaiac negative. An electrocardiogram was normal.

On barium-enema examination the opaque substance passed through the sigmoid and immediately filled the descending colon, cecum and ascending colon concomitantly through a cecosigmoid fistula (Fig. 1). In addition, there was also filling of a segment of ileum in the right lower quadrant and pelvis. On a film taken after evacuation of the barium, the colon had almost completely emptied. There was an irregularly dilated, markedly effaced segment of small bowel overlying the emptied ascending colon. The cecum, after an air-contrast study, appeared markedly deformed and retracted into the region of the fistula, from which an irregular sinus tract appeared to arise and to direct itself into the right side of the pelvis (Fig. 2). On gastrointestinal series the esophagus, stomach and duodenum were normal. The mucosa of the upper jejunum was slightly coarsened, but the barium passed normally through the small bowel as far as the lower ileum. The upper and middle ileal loops were normal in caliber. There was marked irregularity and angulation of the terminal loops of ileum, with obliteration of the normal mucosal pattern. The cecum was retracted toward the midline because of the previously described fistula. There was compression of the medial margin of the cecum and lower ascending colon, evidently by an extrinsic mass. After a five-hour interval all the barium was in the colon except for a few scattered collections in the lower ileum. A plain film of the abdomen

showed a soft-tissue mass with a large, polypoid contour, measuring 9.0 cm. in diameter, lying just to the right of the lumbar spine from the level of the second to the fourth lumbar vertebra. Below this and overlying the sacroiliac joint were ill defined soft-tissue masses, partially outlined by air, and a triangular air pocket just above the right iliac crest. There was some dilatation of at least one loop of small bowel in the left side of the abdomen. A small amount of barium was present in and about the masses.

In the hospital the passage of a large amount of stool and gas decompressed the abdomen. On sigmoidoscopic examination the bowel looked normal. At 20 cm. there was a considerable amount of greenish-gray, mucoid, fecal material coming from above, but no fistulas were visualized.

FIGURE 1. *Barium-Enema Examination.*

The patient was given antibiotics, Amigen and transfusions. On the eighth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. RICHARD WARREN*: The outstanding thing about this abstract is that one third of it is x-ray report. I have tried to come to the case with an open mind, which has been difficult because the clinical description leads us along one track only. I hope Dr. Hanelin will really be able to help me.

*Associate visiting surgeon, Massachusetts General Hospital.

DR. JOSEPH HANELIN: All the barium examinations were done at another hospital, but we have the films and the report. This film of the barium-enema examination shows the filled colon; apparently there was simultaneous filling of the large bowel on both the left and the right — that is, barium passed into the left portion of the bowel normally through the sigmoid and into the ascending colon through what is described as a cecosigmoid fistula. On the film made after evacuation, the bulk of the barium has left the large intestine. A peculiar loop of small intestine, not the colon itself, is superimposed upon the ascending colon (Fig. 1). There is also filling of several loops of small bowel to the left of what appears to be a large right-sided abdominal mass. A sinus tract can be seen extending from the medial aspect of the ascending colon. A double contrast examination done later demonstrates better what appears to be a fistulous tract extending downward from the region of the cecosigmoid fistula (Fig. 2). There is also an irregular band of barium demonstrated on the right side, which may represent either diseased small intestine or another sinus tract. In addition there is delineation of a soft-tissue mass in the right side of the abdomen by virtue of air that surrounds it peripherally; another mass of considerable size below it extends downward into the right pelvis. Barium studies of the small intestine

FIGURE 2. *Double Contrast Examination.*
The lower arrow points to the lower sinus tract. The upper black arrows indicate the mass delineated by surrounding air.

done two days later, from which I have selected two films, disclose a normal upper tract to the level of the lower ileum, where the small-bowel pattern is perhaps slightly disorganized; in the distal ileum we again see about the same picture that was noted in the barium-enema examination — the presence of multiple sinus tracts, a large right-sided abdominal mass and small bowel that appears to be diseased. When the patient entered this hospital, a plain film of the abdomen again demonstrated the right-sided mass, with air above and on the right side of it, and several dilated loops of small bowel. There is also very likely increase in intra-abdominal fluid. The chest examination shows elevation of both leaves of the diaphragm, a small amount of fluid at each lung base and a normal-sized heart.

DR. WARREN: The striking finding is the mass surrounded by air, which is consistent on all films and appears not to be within bowel. It is certainly not within the colon.

DR. HANELIN: It is certainly outside the large intestine; at no time have we completely filled it with barium. I suspect that barium about its periphery delineates the mass, but does not enter it.

DR. WARREN: Can you see a renal pelvis anywhere?

DR. HANELIN: No; nothing suggests a communication with the kidneys.

DR. WARREN: I think there are two problems here; one is to decide what primary disease was causing the trouble, and the other is to decide what queer complication of the primary disease this mass and these bizarre x-ray findings represented.

In a patient who had chronic diarrhea with intermittent obstruction over a period of many years, who had no gastrointestinal bleeding, and who had malnutrition, hypoproteinemia and depletion of certain electrolytes, one can think of one diagnosis only — regional enteritis. When in addition the x-ray films show interintestinal fistulas, and multiple fistulas elsewhere from the ileocecal region, that is the most likely diagnosis to consider. Regional enteritis traditionally has four stages — a stage in which it simulates acute appendicitis, a chronic-diarrhea stage, an obstructive stage and a fistulous stage. This patient had three of these, which is more than one has a right to ask in making a diagnosis.

To mention the possibilities besides regional enteritis, hyperplastic tuberculosis of the ileocecal region is extremely uncommon these days. I think, if one plays the percentages, one is correct in saying that such a condition is not tuberculosis unless there is positive evidence of it elsewhere.

What about chronic appendicitis? We have learned that a mass deforming the cecum can very easily be an inflamed appendix even though the symptoms may be of some chronicity. But these fistulas and this x-ray picture, I believe, are more prominent than one sees with a chronic appendiceal abscess or a chronic inflammatory granulomatous type of appendicitis. It is true that sometimes a patient with regional enteritis will have appendiceal involvement; indeed the onset may be that of an acute appendicitis, and the picture when there have been fistulas and secondary infection may not be as specific for regional enteritis as obtains in the patient in whom such an infection has not developed. Giant-cell granulomas may not be found; there may be only a chronic nonspecific inflammation. So I should think that, although the appendix may have been involved, the disease was not primarily of appendiceal origin.

How about cancer? The chronicity of it is against that; there was no evidence of cancer in the x-ray examination. I cannot rule out cancer secondary to the inflammatory reaction in the bowel, but I have never seen cancer secondary to regional enteritis; I have seen it secondary to ulcerative colitis, and to its cousin, regional colitis, but in the case under discussion the colonic mucosa except at the cecum is relatively normal, and I think I can rule out cancer as the primary disease.

The unusual conditions such as lymphoma I have never seen behave like this or form fistulas. Or if the patient had swallowed a foreign body that had caused a localized perforation in the ileocecal region many years before, a chronic infection could have developed on that basis. Those are outside possibilities that I shall mention but cannot include with any assurance in my clinical diagnosis.

My primary diagnosis, in view of the fact that the patient had an abnormal ileal mucosa and because of the clinical findings, is regional enteritis, with fistula formation and partial obstruction.

What was the peculiar mass that was felt, and what caused this unusual x-ray appearance? I do not know. I assume that the film showed an abscess outside the bowel into which barium had flowed from the intestinal tract, and that the size of the mass was due to the extent of the abscess and its surrounding cellulitis. Why it did not have fluid levels in it and why it was constant in its appearance is more than I can say. There is a possibility that the patient had involvement of the urinary tract with a fistula from the regional ileitis. I have never seen such a case, but fistulas have been reported either into the ureter or into the bladder. I think the safest diagnosis to make is abscess outside the bowel with air from the bowel within it. Another possibility is that the gall bladder was involved. The mass was described as being quite high up, and the tenderness was partially in the right upper quadrant. In many patients with chronic peritoneal sepsis noncalculous cholecystitis will develop. I do not include that as one of my diagnoses, but I think it is another condition that should be listed.

DR. THOMAS PAINE: Have you ever seen amebic infections in that area?

DR. WARREN: I think it would be unusual for amebic infection to be present with a normal colonic pattern.

A PHYSICIAN: What about actinomycosis?

DR. WARREN: I do not know.

DR. BENJAMIN CASTLEMAN: Certainly actinomycosis could do this.

DR. WALTER BAUER: Amebic colitis might do this. Ileocecal fistulas are seen occasionally.

DR. WARREN: A few patients who had amebic infection during the Chicago epidemic later manifested classic regional enteritis.

DR. HANELIN: Amebic infection commonly localizes in the cecum.

DR. CASTLEMAN: But fistulous tracts would be more common with actinomycosis.

DR. JOHN T. QUINBY: Would Dr. Hanelin suggest what might have caused this unusual picture of a mass with air surrounding it?

DR. HANELIN: It could have resulted from either air within a fistulous tract or within the small bowel surrounding the mass.

DR. CASTLEMAN: Dr. Behringer, would you tell us the preoperative findings? Dr. Arthur W. Allen operated on this patient.

DR. GLENN BEHRINGER: Our line of reasoning preoperatively was like Dr. Warren's. We were helped somewhat by the fact that this patient had been studied by a competent gastroenterologist in another hospital five years previously, and a diagnosis of regional enteritis had been entertained at that time. The patient had been well ever since. We thought the most likely diagnosis was regional enteritis. Dr. Stanley M. Wyman, who reviewed the outside films, held out strongly for lymphoma, believing that this polypoid mass seen on the x-ray films was enlarged mesenteric lymph nodes surrounded by a loop of gas-filled or in one film barium-filled bowel.

The main problem was treatment of the subacute small-bowel obstruction, and as soon as the patient was in proper shape for operation one was performed. Two alternatives were considered: one was an internal side-tracking procedure, perhaps an ileotransverse colostomy, and the other, because the barium administered by mouth dropped into the sigmoid and refluxed into the ascending colon, which we thought indicated that the right side of the bowel would not be defunctioned by an ileotransverse colostomy, was an end ileostomy.

CLINICAL DIAGNOSIS

Regional enteritis.
?Lymphoma.

DR. RICHARD WARREN'S DIAGNOSES

Regional enteritis.
Abscess outside bowel.

ANATOMICAL DIAGNOSIS

Malignant lymphoma of small bowel, Hodgkin-sarcoma type.

PATHOLOGICAL DISCUSSION

DR. BEHRINGER: At operation, when about 3 liters of straw-colored fluid had been aspirated and the abdomen was relatively dry, lying just lateral to and perhaps a little above the umbilicus was a large mass about 15 cm. in diameter, which was composed of a greatly thickened, dilated segment of small bowel that was wrapped around a central mass. This inner mass was not disturbed to identify its nature, but it seemed to be enlarged lymph nodes. On the surface of the bowel, which was inflamed and thickened, were orange plaques that appeared to be tumor. It was obvious that there was obstruction at this point because there was collapsed bowel below it. When the bowel was followed upward, it all looked the same and presented some of the features of regional enteritis in that it was thickened, injected and reddish purple and in some areas showed fat growing up over the bowel on the mesenteric side. About 8 cm. above the area where the loop of small bowel was attached to the ascending colon there was a plaque-like area in the antimesenteric wall about 2 cm. in diameter. About 60 cm. above this area was a red-orange, warty tumor mass approximately 4 cm. in diameter that was almost annular, but not constricting. Another such mass was present in the high jejunum, and a loop of jejunum was attached to the posterior parietal wall just beyond the ligament of Treitz. In addition the lymph nodes in the retroperitoneal area were tremendously enlarged. The liver, spleen and gall bladder were normal to palpation. The plaque in the small bowel was removed for biopsy, and a double-barreled ileostomy was performed; the ileostomy was placed at the site of the plaque-like area. The frozen-section report received in the operating room was lymphoma.

DR. CASTLEMAN: The final sections confirmed that this was lymphoma of the Hodgkin-sarcoma variety, which may indicate that the patient had had Hodgkin's disease for some years and that it had changed into Hodgkin's sarcoma more recently. Whether he had had regional enteritis all these years and Hodgkin's sarcoma had developed more recently we cannot tell from the biopsy material. The section of the excised small bowel showed an extensive submucosal and mucosal involvement with malignant lymphoma.

DR. ALFRED KRANES: It was in the bowel wall?

DR. CASTLEMAN: Yes; it was in the bowel wall and almost certainly was in the lymph nodes as well.

DR. GORDON S. DONALDSON: I think in retrospect that this patient probably had had regional enteritis. His symptoms were of long standing, and the growth

of fat was striking. It seemed much more logical to postulate that enteritis had been present for years and that the lymphoma was relatively new.

DR. CASTLEMAN: The same degree of overgrowth of fat would occur with a lymphomatous process in the bowel. That is not a specific finding in regional enteritis; it is just evidence of disease of the small bowel or reaction in the peritoneal fat to intramural disease extending to the serosa.

DR. BAUER: I should like to ask a question that came up at the Medical Service death meeting last night. How long can lymphoma remain confined to the gastrointestinal tract? Five years? Ten years? We know of an occasional case of malignant lymphoma in the gastrointestinal tract proved by surgical excision that upon review had radiographic evidence of a gastrointestinal lesion some years previously. Do you remember any such case?

DR. CASTLEMAN: I can recall one of a few years' duration.

DR. BAUER: It is important to remember such cases when one is dealing with a lesion of this type.

DR. KRANES: Dr. Donaldson has been looking up these cases.

DR. DONALDSON: I do not think I can answer Dr. Bauer's question. Dr. Leland S. McKittrick had a patient with malignant lymphoma of the stomach proved by biopsy who lived for six years, but he was given x-ray therapy and later died of his disease. The course of lymphoma, on the other hand, can be dramatically rapid. In the hospital series one patient is still alive twenty-one years after resection of a gastric lymphoma.

DR. WILLIAM H. BAKER: Malignant lymphoma is notorious for its unpredictable course. We are at present reviewing all the cases here with survivals beyond ten years. At present we have surveyed over 30 such patients, and it is interesting that the commonest lesion we have encountered is lymphoma confined to the gastrointestinal tract.

DR. WARREN: How is the patient?

DR. BEHRINGER: Aside from the hypoproteinemia, he has done very well.

DR. WARREN: It would be helpful to know whether that mass in the x-ray film was a bunch of enlarged lymph nodes surrounded by air.

DR. BEHRINGER: I am sure a hollow viscus contained the air and was wrapped around enlarged mesenteric lymph nodes, with fistula into the adjacent colon. We could see no evidence of abscess although the mass was not disturbed too much. The course was not febrile.

CASE 39212

PRESENTATION OF CASE

First admission. A fifty-seven-year-old man was admitted to the hospital for bronchoscopy.

No details of the clinical history were available. Physical examination revealed that the inferior half of the right lung was dull, with decreased breath sounds and decreased tactile fremitus. The temperature ranged between 100° and 102°F. Roentgenograms of the chest demonstrated a mottled infiltration in the right lower lobe of the lung (Fig. 1). At bronchoscopy on the second hospital day a tumor was found just below the bifurcation occluding the lumen of the right main bronchus. This apparently had sprung from the region of the right-upper-lobe orifice. It had a smooth surface, bled easily and seemed freely movable as though it had a pedicle. During the attempt to biopsy the mass with the punch forceps, pressure from the bronchoscope seemed to detach the mass, which was then coughed out in its entirety. Microscopical examination of this mass revealed it to be squamous-cell carcinoma, Grade 4. Two days later the patient's temperature returned to normal; he felt much better and was discharged. During the following month he received x-ray treatment, a total of 6000 r, to the area over the right main bronchus, and the mottled infiltration in the lung noted in the x-ray film disappeared (Fig. 2).

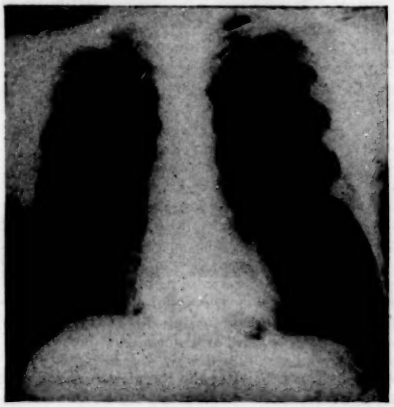

FIGURE 1.

Second admission (about eight years later). The patient was not seen again until four and a half months before this admission, when he reported to the Tumor Clinic complaining of a sore throat of several months' duration. Examination revealed an irregular ulcerating growth involving the right tonsil, with extension to the anterior pillar and the base of the tongue. No cervical lymph nodes were palpable. Roentgenograms of the chest showed no appreciable change in the appearance of the lung fields since the

first admission except for some fibrosis at the right hilus. Biopsy of the ulcerated area was reported as showing squamous-cell carcinoma, Grade 2, and the area was given x-ray treatment, 6000 r, over the next month, with marked regression of the tumor. The patient was followed regularly in the Tumor Clinic for the next few months, and no sign of local recurrence or of metastasis was noted. Four

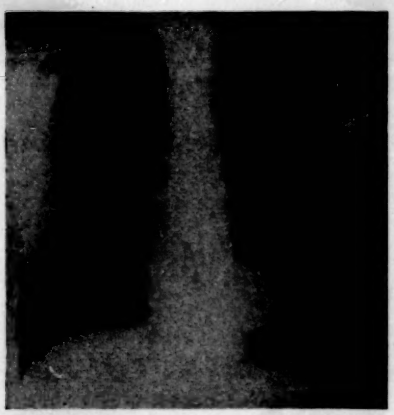

FIGURE 2.

and a half months after the completion of radiation therapy, he had a recurrence of the tumor in the right tonsillar area, proved by biopsy, and was admitted to the hospital.

During this admission excision of the area of the right tonsillar fossa with electrocautery was carried out. Microscopical examination of the excised tissue showed marked chronic inflammation with no evidence of cancer. The patient was discharged in good condition.

Third admission (several days later). Several days after discharge he was readmitted to the hospital because of difficulty in swallowing that had led to dehydration. However, this soon cleared up with intravenous fluid therapy and antibiotics.

Fourth admission (about three months later). At this time the patient was found to have another recurrence of the tumor in the region of the lateral pharyngeal wall for which a resection of most of the soft palate, including the mucous membrane near the eustachian orifice and the right tonsillar fossa, was carried out with electrocautery. Microscopical examination of the excised tissue showed squamous-cell carcinoma, Grade 3.

Fifth admission (about eighteen months later). Two months after the fourth admission, when he was seen in the Tumor Clinic, a small ulcer was noted above the orifice of the right eustachian tube. During the next month x-ray therapy, 4000 r, was delivered to this area. Eleven months later another ulceration was noted near the eustachian-tube orifice on the right side, biopsy of which was reported as showing squamous-cell carcinoma. Over the next month he received a 3700-r tumor dose. About this time he began to complain of some pain in the left side of the chest, but a roentgenogram demonstrated no apparent change in the lung fields. During the next two or three weeks his appetite

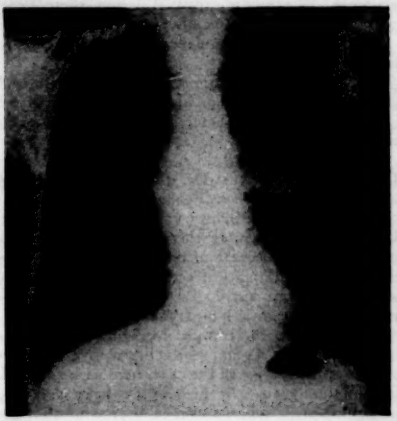

FIGURE 3.

decreased markedly; he became mentally depressed, and admission was advised.

Physical examination revealed marked atrophy and fibrosis of the right lateral pharyngeal wall up to the eustachian-tube orifice. It was noted that the left vocal cord did not move whereas examination two years before had shown that both cords moved well. No lymph nodes were palpable in the neck. A roentgenogram of the chest disclosed some infiltration in the apical part of the left lower lobe that was regarded as possibly due to aspiration (Fig. 3). The patient was treated with penicillin, with some clinical improvement. However, a chest x-ray film taken two weeks later while he was still in the hospital showed that cavitation had developed in the apical segment of the left lower lobe. A sputum smear was negative for acid-fast bacilli. At bronchoscopy the right bronchus and carina appeared

normal. In the left-lower-lobe region of the left main bronchus there was marked redness, and an appearance suggestive of granulation tissue was noted along the floor. A smear of the washings from this area was reported as positive for tumor cells. Nevertheless, the cavity continued to decrease in size, and the patient's clinical condition improved. He was discharged on penicillin for the Christmas holiday season after having been in the hospital for about three weeks.

Sixth admission (two weeks later). The patient was readmitted to the hospital for study. Another roentgenogram of the chest showed that there had been marked clearing of the process in the left lower lobe. He was discharged on the day after the bronchoscopy.

Seventh admission (five days later). He was readmitted to the hospital for x-ray treatment to the region of the left main bronchus. During this admission there was no gross evidence of recurrence of tumor in the region of the right tonsil or eustachian tube. No cervical lymph nodes were palpable. The patient was kept in the hospital for a week and discharged to have treatment continued on an outpatient basis.

Final admission (about ten days later). On the eighteenth day of treatment the patient, who had been given 4800 r to the region of the left main bronchus, had a severe bout of hemoptysis during which he coughed up a basin full of blood. He was admitted to the hospital in shock; the hemoglobin was 9.2 gm. per 100 cc. Over the next two days he had no more bleeding, but on the third hospital day he suddenly coughed up a large amount of blood and died within a few minutes.

Differential Diagnosis

Dr. William H. Baker*: I assume that 6000 r was tumor dose.

Dr. Richard Schatzki: It probably was not recorded as tumor dose over ten years ago.

Dr. Baker: In summary this is the case of a sixty-four-year-old man whose respiratory tract constituted a fertile field for the development of neoplastic disease but whose body was able to survive this neoplastic disease for approximately eleven years. I think, for the purpose of clarity, that it is best to separate this man's illness into three phases, the first phase being the period during which the primary lung cancer in the right upper lobe developed. I am somewhat confused about the therapy after the diagnosis of the tumor. I think that at present surgical rather than x-ray therapy would probably be recommended. The tumor itself appeared localized. I wonder whether the surgeons declined to operate because of the grade of malignancy (Grade 4) or whether the bronchoscopist convinced them that the entire tumor had been dislodged. At any rate, the patient was given x-ray therapy, which achieved an excellent result. There are other patients with inoperable lung cancers who have been treated with large amounts of x-ray therapy and have survived for long periods. The most recent report appeared in November, 1952.[1] Thus, the statement that x-ray therapy is merely a palliative measure in the treatment of lung cancer is not 100 per cent true.

The second phase of the illness began when a tumor developed in the right tonsillar area at the base of the tongue. Clinically, this area is much frequented by a type of tumor known as transitional-cell carcinoma. The ratio of transitional-cell tumors to squamous-cell carcinoma is about 1:10 in this area, but the good response to x-ray therapy is more consistent with transitional-cell carcinoma. The absence of palpable lymph nodes and the fact that the pathological specimen was diagnosed as squamous-cell carcinoma obviously rule out transitional-cell carcinoma. Over the next three years, x-ray therapy and subsequently surgical therapy was given for a tumor that recurred intermittently during that period.

The main problem in this case is the third phase of the illness: the development of infiltration in the left-lower-lung field. Associated with this infiltration was a left-vocal-cord paralysis, which I think constitutes pertinent information for the diagnosis. Vocal-cord paralysis is much more consistent with the diagnosis of tumor than with the diagnosis of lung abscess, mycotic infection or any other type of infection in the lung. Yet it was obvious in the x-ray films that this patient had a lung abscess. He was treated with penicillin, with a good response. There is no reason to rule out carcinoma merely because the lung abscess grew smaller with penicillin therapy. As a matter of fact lung abscess occurring in any elderly patient should always be suspected of being bronchogenic carcinoma. May I see the x-ray films now?

Dr. John F. Gibbons: The films were all of the chest. The first set, made at the time of the original admission, eleven years before the final admission, demonstrates a mottled infiltration in the right lower lobe (Fig. 2). There is an old scar, probably the result of old tuberculosis in the right upper lobe, that has caused slight elevation and probably a slight decrease in size of the right upper lobe. The hilar shadows do not appear particularly enlarged, and there is no evidence of disease in the left side of the chest or of enlarged lymph nodes. About six weeks later, after a bronchoscopic examination and removal of the tumor had been carried out, most of the infiltrative process in the right lower lobe has cleared, and the lungs are virtually clear (Fig. 2). In the films seven or eight years later, at the time of the second admission, there is retraction of the mediastinal structures to the right side and more elevation of the hilar shadow,

*Clinical and research fellow in medicine, Massachusetts General Hospital.

with an area of fibrosis that is presumably the result of the previous course of x-irradiation.

DR. BAKER: Is the trachea deviated?

DR. GIBBONS: The trachea is pushed over at this time as the result of the fibrous traction. As far as one can tell the left-lung field is still clear, and there is no detectable change in the left hilar region. Then the patient had several films over the next few months in the Eye and Ear Infirmary. One six months and one nine months later showed no change. On the film taken at the time of the fifth admission, when the pain had developed in the left side of the chest, the area of mottled density is again noted in the left-midlung field (Fig. 3).

DR. BAKER: How was that interpreted?

DR. GIBBONS: It was interpreted as being pneumonitis, probably secondary to aspiration. At that time the patient had the vocal-cord paralysis, and no other diagnosis was made. The films taken during the next two weeks show cavitation developing, and in the lateral view the abscess is seen in the posterior segment of the left lower lobe. There is no evidence of gross collapse of any segment of the left lung. (Over the next few weeks with antibiotic therapy the abscess became smaller and was practically obliterated at the time of the last film, which was taken shortly before death.) At no time since the second admission has there been any change or evidence of collapse in the right lung or any change in the size of the left hilar shadow, so that from the roentgenographic standpoint the process in the left lung seems to be primarily an inflammatory process. Whether it is distal to an area of tumor-bearing bronchus we cannot say; we have no evidence for that.

DR. BAKER: Do you think that the apexes are clear?

DR. GIBBONS: I think that there is scarring in the right apex and thickening of the pleura, probably as the result of the healed tuberculosis.

DR. BAKER: The main problem here seems to be the characterization of the terminal phase of this man's illness. Certainly, this abscess could have been tuberculosis. He had old tuberculous scarring in both apexes and old lesions in the right side of the chest that could well have been the source of tuberculosis. During x-ray therapy there was a dramatic change terminally, with possible erosion and rupture of a major vessel and death, all of which are consistent with tuberculous abscess. The sputum was negative for tubercle bacilli, but one negative examination does not rule out tuberculosis. Therefore, there was no really positive evidence against tuberculosis. The best way to rule out tuberculosis is to make a positive diagnosis of another disease. The diagnosis of mycotic infection of the lung — such as actinomycosis or something more exotic than that — seems unlikely. I have no evidence for any of these diseases. No sulfur granules were observed on bronchoscopic examination, and there was no evidence of them elsewhere.

The major portion of the evidence adds up to the fact that the likeliest cause of this man's lung abscess is obstruction. The obstruction could have been due to an aspirated foreign body such as a peanut, but there was no history of that. Bronchial adenoma could cause this condition but as far as I know — and I have asked Dr. Edward D. Churchill about this — to date there have been no bronchial adenomas that have had a positive Papanicolaou smear; often, the smear is reported as doubtful. There have been, however, false-positive cytologic smears in other conditions. Nobody seems to know the exact percentage of false-positive smears that occurs because the patients have not been followed long enough or have not died. The accuracy of the Papanicolaou test in the diagnosis of bronchogenic carcinoma at this hospital is somewhere between 40 and 60 per cent; the accuracy is much higher with sputum examinations than with bronchial aspirations because the sputum examinations are usually done on more than one sample at a time when the patient has symptoms with a productive cough. The terminal event was a large pulmonary hemorrhage, which I consider to have been due to an erosion of a major vessel from a neoplastic process.

This patient probably had three distinct separate tumors: the first in the right-upper-lobe bronchus, the second in the oral cavity, and the third in the left lower lobe. It is extremely difficult to be sure because the first two tumors were the same type and the third may also have been squamous-cell carcinoma. It would be much more helpful to have histologic evidence of different types of neoplasm. I do not believe that one can ever say, when morphologically they are all squamous-cell carcinomas, that they are distinct tumors. The tonsil and the tongue are unusual sites for a metastasis from a bronchogenic tumor; however, notoriously, bronchogenic carcinoma metastasizes to any organ in the body. I base my decision that this was bronchogenic carcinoma mainly on the facts that the patient had a vocal-cord paralysis, that there was a positive smear on material obtained from the region of the involved lobe and that he had had two previous tumors. This point of the two previous tumors is quite important. Warren, Gates and Ehrenreich[3, 3] pointed out that tumors occur eleven times more frequently in patients who have previously had tumor than in patients who have not had a tumor and that the appearance of multiple tumors is approximately 6.8 per cent. Cahan,[4] discussing multiple tumors, recently reported that in a total of 25 cases of lung tumors associated with other tumors, 7 patients had oral carcinomas as well.

In summary my diagnoses are carcinoma of the right lung, with a ten-year "cure," carcinoma of the oral cavity, arrested and probably cured by x-ray therapy and surgery, and carcinoma of the left-

lower-lobe bronchus, with abscess formation. I hope if this turns out to have been a carcinoma that Dr. Castleman will call it an adenocarcinoma and not a squamous-cell carcinoma.

A PHYSICIAN: Would you consider it possible that the positive sputum was secondary to the radiation?

DR. BAKER: You mean sloughing off of tissue as the result of the radiation. I should think that would be highly unlikely. The patients with false-positive sputum smears whom Dr. Churchill cited to me had no evidence of any disease. Those patients are still being followed, and Dr. Churchill does not know whether they have carcinoma or not.

DR. EDWARD B. BENEDICT: I cannot believe that the carcinoma of the right main bronchus was completely coughed up. I should think it much more likely that it recurred and invaded the left lung. The carcinoma in the pharynx might have been a separate primary tumor.

DR. BAKER: That certainly would be difficult to determine if this turns out to have been a squamous-cell carcinoma of the left lung. It could have been metastatic from the right lung eleven years before. Most of those patients do not survive that long; that is more in keeping with a thyroid carcinoma or a breast carcinoma. It would be unlikely for a tumor of the right lung to metastasize to the bronchial tube and cause obstruction.

DR. JACOB LERMAN: I should like to ask Dr. Schatzki this point. We assume this was an ordinary lung abscess; would this much radiation cause an area of that sort?

DR. SCHATZKI: That is difficult to answer; I doubt that it would.

DR. BAKER: Was the patient a smoker?

DR. J. B. TALLON: He had smoked about two packages of cigarettes a day for years.

CLINICAL DIAGNOSES

Carcinoma of left lower lobe of lung.

Carcinoma of right lateral pharynx.

Healed carcinoma, right upper lobe of lung (ten years).

DR. WILLIAM H. BAKER'S DIAGNOSES

Carcinoma of left lower lobe of lung, with abscess formation.

Carcinoma of right lung, with ten-year cure.

Carcinoma of oral cavity, probably cured.

ANATOMICAL DIAGNOSES

Squamous-cell carcinoma of left lower lobe, with erosion of pulmonary artery and massive pulmonary hemorrhage.

Squamous-cell carcinoma of pharynx, irradiated.

Squamous-cell carcinoma, pedunculated, right upper lobe bronchus, aspirated ten years before admission.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The slide of the tissue removed in 1942 had been presented to the pathologist for review every other year — every time the patient entered the hospital — to be sure that it really was a squamous-cell carcinoma because there was no evidence on x-ray examination over the ten-year period that there was anything on the right side. There is no doubt in my mind that this was an undifferentiated squamous-cell carcinoma that this man coughed up, and I believe that he did cough up the whole tumor. The surface of the tumor coughed up was necrotic, and beneath the necrotic area were very highly undifferentiated squamous cells; in one or two areas, however, there was a well differentiated, keratinized pearl. At the time of autopsy the trachea and the right main bronchus looked very smooth; there was no semblance of any irregularity — and multiple blocks taken for microscopical examination gave no evidence of any tumor. I see no reason why a pedunculated tumor in the bronchus, even if it was a squamous-cell carcinoma microscopically, could not have been coughed up completely. The x-ray treatment may have had something to do with the cure, but I doubt it.

The immediate cause of death was quite obvious; the patient had hemorrhaged into the lung and drowned. On the left side in the main bronchus to the lower lobe, we found an obviously granular irregular area that proved to be a squamous-cell carcinoma; the tumor puckered the adjacent pulmonary artery, and although we could not find an actual erosion in the artery, I am fairly sure that it was the site of the terminal hemorrhage. A section through the right eustachian area showed a small amount of the cancer left.

Of course, one cannot rule out the possibility that the recent cancer in the left-lower-lobe bronchus was not a metastasis from the oral lesion; I believe that it had nothing to do with the original lesion.

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QUALIFICATIONS FOR SERVICE

THE letter of Dr. Magnuson published elsewhere in this issue of the *Journal* presents a problem that, while perhaps not unique in Massachusetts, is particularly important here because of the existence in the Commonwealth until recent years of substandard schools of medicine. These schools, although now disfranchised, have left a number of graduates legally licensed to practice medicine in the State, most of them gaining in experience and skill as time passes, and many of them already fellows of the Massachusetts Medical Society.

This increased personal usefulness is most evident in those communities where the medical fraternity itself, instead of ostracizing such legally qualified practitioners, has been interested in drawing them into the circle and giving them a helping hand. The Gallupe Plan has been the most conspicuously successful of these efforts of established physicians to help their colleagues with less orthodox training rather than abandoning them and their patients to the isolated exercise of the skills that they may have acquired.

The attitude of the armed forces in disqualifying graduates of substandard schools from military service is a matter of concern, both as it reflects on the capacity of these physicians to serve their country, and shifts the burden of such service entirely onto their educationally more favored colleagues. A federal agency in its selection of personnel can scarcely consider states' rights to the point of binding itself to the observance of forty-eight separate standards of education. The action in this situation, on the other hand, seems particularly unfortunate in view of the circumstances as outlined in Dr. Magnuson's letter. A major inconsistency is the fact that the class of physicians now excluded was found acceptable when the need was greatest and when many of them were, in all probability, not as qualified to serve as is the group now available.

INFLUENZA A′ AND CONGENITAL ANOMALIES

GREGG's[1] revelation of the effect of rubella in pregnancy more than a decade ago gave an impetus to the exploration of the causes of congenital malformations that continues in various directions. A century earlier Jonathan Hutchinson had observed that prenatal syphilis might result in interstitial keratitis, implying the same relation as rubella and cataract; however, these implications of the Hutchinsonian triad, which should have pointed the way to acquiring broader knowledge of other influences acting on the fetus during pregnancy, were regarded too narrowly in terms of the specific venereal disease involved. In the last ten years the problem has been considered more actively in the laboratory than in the field, so cumbersome is the task of case finding, follow-up study, classification of defect and centralization of data when ordinary state or hospital records are utilized.

An important principle that has emerged from the independent laboratory studies of several investigators is the demonstration that a particular defect such as cleft palate can be induced by various unrelated agents — vitamin deficiencies, anoxia, cortisone injections and x-rays — provided that their impact is of critical degree and registered while the palate is forming. The age-old, almost superstitious, belief that such an anomaly has a single hidden cause is obviously false. A concept of critical stress takes its place, with specificity decided more by the embryonic host than by the injurious agent.

The present challenge is to assemble more quantitative information in human populations. The first step is to explore a hypothesis that a particular infection — influenza, for example — accounts for a significant number of cases of deformity in the babies of a group of mothers at risk. The beginning is ordinarily made retrospectively. The technic may be illustrated by the demonstrations of the relation of postrubella cataract and deafness to infection in the second and third months of pregnancy. Significance of a hypothesis, formulated in retrospect, is established by the timing of the causative insult during pregnancy. If German measles stands in no causative relation to cataract it is difficult to see why it should generally precede cataract in the second month of pregnancy — the time at which the lens fibers of the eye are undergoing differentiation — and not be distributed throughout pregnancies that result in this form of blindness.

The second step, more difficult to accomplish in the field for reasons that are obvious, is to follow the stressing agent prospectively (the so-called "follow-up study") and to observe its effect on the baby. Last July the *Journal* undertook this kind of inquiry[2] for rubella in an attempt to communicate with obstetricians before reporting was biased by a knowledge of the outcome. The results were very encouraging, 20 initial and follow-up reports having been received; analysis is now being made, and the data will be presented in the near future.

Meanwhile an outbreak of influenza A′ swept the northeast section of the United States during the first months of 1953, and this situation presents a fleeting opportunity to attempt to ascertain whether that condition does or does not affect the unborn child. To seize this opportunity without further delay another questionnaire, which is presented in Medical Intelligence in this issue of the *Journal*, attempts to interest directly the physicians who are caring for these mothers as well as those who subsequently examine the newborn infant. The response to the query on rubella — and that is a rare complication of pregnancy — exceeded expectation. In the present investigation the response should result in the accumulation of many more data, for when the disease is present it spares few, regardless of sex or the presence of pregnancy.

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FATHER OF INDUSTRIAL MEDICINE

The British *Transactions of the Association of Industrial Medical Officers* contains each month or thereabouts a special section under the title "The World Outside the Factory." The very naming of this section is a pleasant reminder that a world outside the factory has come, during the past century, actually to exist for the factory worker. This extramural environment was hardly available to the original beneficiaries of the Industrial Revolution nor to their heirs for a long time after it.

A variety of interests for the industrial medical officer also appears in this world outside the factory; in the issue of July, 1953, a dissertation by Dr. Charles C. Sutherland, the eminent London authority on occupational diseases, is found concerning the original classic on industrial medicine — *De Morbis Artificum Diatriba*. This "diatriba," literally a "learned discussion," not "a bitter or abusive harangue" as later lexicographers define it, was published in 1700, having come from the pen of Bernardino Ramazzini. Its most recent translation, by Wilmer Cave Wright, late emeritus professor of Greek at Bryn Mawr College, appeared in 1940.

Ramazzini, appropriately called the Father of Industrial Medicine, had been for twenty-two years professor of the theory of medicine at Modena

when the *Diatriba* was published; he later moved to Padua, where he occupied the equivalent chair. According to William Farr, the English exponent of vital statistics a century ago, it was the diatribe that put Modena on the medical map; modern Modena, however, seems to have forgotten Ramazzini — a form of amnesia not without precedent in the history of human relations.

Ramazzini's work was published in two editions, the second appearing in 1713 and containing 12 supplementary chapters. The first English translation, called *A Treatise of the Diseases of Tradesmen*, appeared in 1705. It received some attention, for in an August, 1713, number of the *Guardian*, successor to the *Tatler* and the *Spectator*, reference was made to "a treatise written by a learned physician on the distempers peculiar to those who work in stone and marble."

A second translation by Dr. Robert James, a practitioner of Sheffield, was published in 1746. It appears, however, according to Professor Wright, that Dr. James translated the supplementary chapters, added them to the 1705 translation and published the result as the legitimate offspring of his own intellectual processes.

As a slight digression from the diseases of tradesmen, Dr. James's real claim on posterity might be mentioned. It lay in his invention of that mixture of phosphate of lime and oxide of antimony known forever after as James's Powders and entered in the British Pharmacopoeia as *Pulvis Antimonialis*. This powder is said to have been called for by Goldsmith in his last illness, perhaps with unfortunate results; an episode so captivating to the imagination that it inspired a booklet on *An Account of the late Dr. Goldsmith's Illness so far as it related to the exhibition of James's Powders*.

Despite the liberties that have been taken by translators, with or without powders, the fame of Ramazzini as the paternal ancestor of industrial medicine seems secure.

Dr. Sutherland having ended his own essay with a simple "Thank you, Professor Wright," so let this annotation come to a similar conclusion with an equally sincere "Thank you, Dr. Sutherland."

"HAPPY EVENT"

A LITTLE late, but better late than never, respectful attention is directed to an important medical event the hundredth anniversary of which fell on April 7 of this year. The *British Medical Journal*, in a leading article published on April 11, announced the anniversary of this happy event by reprinting an announcement from the *Court Circular* of April 7, 1853, to the effect that, at Buckingham Palace, "At ten minutes past one o'clock this day the Queen was safely delivered of a prince."

The importance of the event was not so much the birth of another heir, Leopold being Victoria's eighth child, as it was the fact that on this occasion the Queen consented to the administration of chloroform. By this consent she established a precedent that helped to overcome the religious and professional objections that had until that time prevailed.

Despite the disapproval of the *Lancet* — "uncharacteristically behind the times," as the *British Medical Journal* now graciously phrases it — the *Association Medical Journal* of that time gave the scientific and humanitarian procedure its full approval:

> The responsible position, and the acknowledged skill of the physicians who sanctioned the inhalation of the chloroform, the Royal Majesty of the patient, and the excellence of her recovery, are circumstances which will probably remove much of the lingering professional and popular prejudice against the use of anaesthesia in midwifery, even when sanctioned by competent authority, and induced with requisite precaution. It is for this reason that we chronicle the recent accouchement of Her Majesty as an event of unquestionable medical importance.

The clamor of the clergy against this parturient employment of anesthesia, with the invoking of the Biblical injunction that "in sorrow thou shalt bring forth children," will be recalled. It was countered by the sagacious churchman who pointed out that the Lord had already caused a deep sleep to fall upon Adam before delivering him of his well known and somewhat troublesome rib.

Norfolk District Medical Society. — *The Society voted to have a general discussion of the prevailing diseases of the autumn at the next semi-annual meeting in November.*

Boston M. & S. J., *May 25, 1853*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

DALY — Jeremiah J. Daly, M.D., of Andover, died on April 19. He was in his seventy-eighth year.

Dr. Daly received his degree from Tufts College Medical School in 1903. He was a member of the board of health of Andover.

He is survived by his widow, one son, two daughters, a sister and seven grandchildren.

DELAND — Charles A. DeLand, M.D., of Warren, died on April 26. He was in his ninety-fourth year.

Dr. DeLand received his degree from Harvard Medical School in 1885. For forty years he was medical examiner for the Brookfield-Warren District. He also served on the staffs of Mary Lane Hospital in Ware and Wayne Memorial Hospital in Palmer. He was a retired fellow of the American Medical Association.

He is survived by two daughters, a son, two grandchildren and six great-grandchildren.

DENORMANDIE — Robert L. DeNormandie, M.D., of Lincoln, died on April 20. He was in his seventy-eighth year.

Dr. DeNormandie received his degree from Harvard Medical School in 1902. He was formerly president of Suffolk District Medical Society, instructor in obstetrics at Harvard Medical School, chairman of the board of the Tewksbury State Hospital, a member of the staff of Boston Lying-in, Faulkner, New England Baptist and Waltham hospitals, medical consultant to the Maternal and Child Welfare Division of the United States Public Health Service and chairman of the Lincoln board of health. He was a member of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons and a fellow of the American College of Surgeons and American Medical Association.

He is survived by his widow, a son, two daughters and eleven grandchildren.

CORRESPONDENCE

UNFORTUNATE RULING

To the Editor: The recent refusal of the armed forces to induct graduates of substandard schools is the background for a situation in New Bedford, and therefore in Massachusetts as a whole, that is rightly the concern of the Massachusetts Medical Society. Possibly Massachusetts is unique in having this problem, and probably the federal authorities are unaware of its ramifications. Certainly, it has in recent weeks touched off locally in New Bedford lively sentiments that are unhealthy and disturbing to doctors and hospitals alike.

The graduate of a substandard school is given the privilege of practicing medicine in Massachusetts. He is given the honor of membership in the state medical society. In recent years, together with the closing of the substandard schools, pressure has been exerted politically and by the Massachusetts Medical Society on hospital staffs to open their doors to these men. By and large in New Bedford this has proved a beneficial move to both patients and doctors, and therefore to the community; it has been found that there are good men from substandard schools as well as poor men from accepted schools. As for duty in the armed forces the graduate of the substandard school was commissioned during the latter part of World War II and until very recently was still acceptable for such service; there seems to have been a change in policy, the reasons and mechanics of which are not public knowledge.

In this city of 130 physicians, 40, or nearly 27 per cent, are from substandard schools. Assuming that the percentage holds throughout the State and that the number of doctors requested for service depends on the total number in a state, the Massachusetts graduates of accepted schools must contribute disproportionately more in numbers than physicians in any other state. It is perhaps this feeling of impending "greeting" by the federal Government on the part of veteran physicians that has excited so much heated comment in New Bedford, for, if the present rate of refusals for the graduate of the substandard school and for the physically disqualified graduate of an approved school continues, it becomes very logical to wonder, "Who will go?"

The situation poses several questions. Is this ruling a Public Law of Congress, a variable policy of the Defense Department, or an Executive order? Why is it applicable in some but not in all cases? Is it logical to allow a physician to practice in civil life but not in a civilian army? As a corollary, is it also logical for approved hospitals to continue men from substandard schools on their staffs? Can the armed forces suddenly find no position for a medical officer with mediocre training, when it is obvious that there are many assignments in the services where the pen is mightier than the stethoscope?

The present state of world affairs requires large armed forces; the reaction of the average citizen, medical and otherwise, is not, unfortunately, one of patriotism, as in all-out war, but of unpleasant necessity. Since the medical profession as a group must be subject to draft, rightly and necessarily so, the official voice of the profession (the medical society) should assume some responsibility for seeing that it is a draft sensible in logic and equal in application.

PAUL MAGNUSON, M.D.

New Bedford, Massachusetts

CONCERNING PRIORITIES

To the Editor: I wish to comment on the recent communications printed in the *Journal* concerning the doctor draft. It seems to me that previous length of service is merely a secondary consideration in determining priority of draft call. The only equitable basis for selection is the type of prior service. Casualties among doctors are extremely rare. Although the doctor draft is discriminatory legislation, medical officers enjoy a privileged position of relative safety from a battalion aid station on back to other rear units. For this reason I have no sympathy for any of the complaints offered by various doctors about inequities in the draft law. Only men who have served in line units should be exempt from any further service. All doctors without prior service in a line unit should be subject to draft call as they are needed, with prior length of service only a minor consideration.

Regarding the "disadvantages and hardships" of the ASTP group — this is hardly more than amusing. I think that the ASTP-trained physicians should be especially liable to the draft. Several years of service is but a small price to pay for a free medical education and a medical degree obtained while some of their countrymen were dying.

LEONARD ATKINS, M.D.

Boston

To the Editor: Reading the letters in the April 16 issue of the *Journal*, I can understand the concern of physicians who have served slightly less than twenty-one months in the armed forces and who are now being called up for an additional seventeen or twenty-four months. However strong their case may be, it does not get at the crux of the present doctor draft legislation, which in my opinion is: What are the specific military obligations of the doctor both as a professional man and as a citizen under the present limited emergency? Neither the present law nor proposed legislation answers this question.

It is necessary for the continued high standards of medical practice and science that discriminatory legislation against the medical profession be eliminated — though at the same time the obligations of citizenship be accepted by all members of the profession. This could be accomplished if physicians previously deferred because of alleged essentiality or medical-school or advanced training now serve. Their employing institutions should co-operate with them by no longer requesting their deferment. Their places could reasonably be expected to be filled by those who have already served, and thus the medical profession would be accepting the obligation of service without the necessity for discriminatory legislation and at the same time maintain continued service to medical education and the community.

P. HERBERT LEIDERMAN, M.D.

Harvard Medical School
Class of 1953

MISCELLANY

NEW ENGLAND SOCIETY OF PSYCHIATRY

The following physicians were elected officers of the New England Society of Psychiatry at its annual meeting held at the State Hospital, Concord, New Hampshire, on April 22: president, Edgar C. Yerbury, M.D., of Middletown, Connecticut; vice-president, John L. Smalldon, M.D., of Concord, New Hampshire; secretary-treasurer, Peter B. Hagopian, M.D., of Boston, Massachusetts; and councilors, Winthrop Adams, M.D., of Bedford, and Arthur H. Ward, M.D., of Framingham, Massachusetts.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Grundlagen der Röntgendiagnostik und Röntgentherapie. By Prof. Dr. G. Schulte, and Prof. Dr. F. Kuhlmann. Third revised edition. 8°, cloth, 298 pp., with 331 illustrations. Stuttgart: Georg Thieme, 1952. DM 29.70. (Distributed by Grune and Stratton, New York.)

This new edition of a work on roentgendiagnosis and therapy, first published in 1939, has been revised and brought up to date. The text is divided into two parts: diagnosis and therapy. The material in both parts is arranged by organs and systems. The book is a personal one, reflecting the experience of the authors. There is a good index, and the publishing is excellent.

Sterility: Its cause and its treatment. By J. Jay Rommer, Ph.G., M.D., member, Gynecological Staff, Beth Israel Hospital, Newark, New Jersey. 4°, cloth, 424 pp., with 152 illustrations and 21 tables. Springfield, Illinois: Charles C Thomas, 1952. $12.50.

This new book on sterility discusses the subject in a comprehensive manner, including the fundamentals of reproduction, the causative factors, pathology and treatment. Lists of references are appended to the chapters and there is a good index. The book is recommended for all medical libraries.

Living in Balance. By Frank S. Caprio, M.D. 8°, cloth, 246 pp. Washington, D.C.: Arundel Press, Incorporated, 1951. $3.75.

This book, evidently written for the laity, discusses various types of neurotic persons, with suggestions concerning self-treatment, with the objective of attaining a balanced mental life.

Battle Casualties: Incidence, mortality, and logistic considerations. By Gilbert W. Beebe, Ph.D., Division of Medical Sciences, National Research Council; and Michael E. DeBakey, M.D., professor of surgery, Baylor University College of Medicine. 8°, cloth, 277 pp., with 37 illustrations and 100 tables. Springfield, Illinois: Charles C Thomas, 1952. $10.50.

This monograph deals with the incidence of hits and wounds, death from wounding, effectiveness of weapons, location of hits and wounds, and logistic problems of personnel, hospitalization and evacuation in forward areas. Five appendixes are devoted to statistics of hospital days and admissions. The text is illustrated with 100 tables. There is a good index, and the publishing is excellent in every way. The book should be in all collections on military medicine and traumatic surgery.

Logan Turner's Diseases of the Nose, Throat and Ear. Edited by Douglas Guthrie, assisted by John P. Stewart. Fifth edition. 8°, cloth, 478 pp., with 246 illustrations and 9 colored plates. Baltimore: Williams and Wilkins, 1952. $8.00.

In its present form this book has gone through five editions and twelve printings since 1924. The fourth revised edition was published in 1936. This new edition has been thoroughly revised and brought up to date. New material includes penicillin and the sulfonamides, disorders of the voice, teaching of the deaf and artificial aids to hearing and to modern advances in endoscopy. There is a good index, and the publishing is good.

Studies from The Rockefeller Institute for Medical Research: Reprints. Vol. 142. 4°, paper, 635 pp. New York: The Rockefeller Institute for Medical Research, 1951. $2.00.

Studies from The Rockefeller Institute for Medical Research: Reprints. Vol. 143. 4°, paper, 615 pp., with illustrations. New York: The Rockefeller Institute for Medical Research, 1952. $2.00.

Studies from The Rockefeller Institute for Medical Research: Reprints. Vol. 144. 4°, paper, 609 pp., with illustrations. New York: The Rockefeller Institute for Medical Research, 1952. $2.00.

A Status Report on Atomic Energy. By T. Keith Glennan, Commissioner, United States Atomic Energy Commission. 4°, paper, 14 pp. Washington, D.C.: United States Atomic Energy Commission, 1952.

Stereoencephalotomy: Thalamotomy and related procedures. Part I, Methods and Stereotaxic Atlas of the Human Brain. By E. A. Spiegel, M.D., professor of experimental and applied neurology and head, Department of Experimental Neurology, Temple University School of Medicine and Hospital; and H. T. Wycis, M.D., clinical professor of neurosurgery, Temple University School of Medicine and Hospital. 4°, cloth, 176 pp., with 79 illustrations. New York: Grune and Stratton, 1952. $7.75. (Monographs in Biology and Medicine, Vol. 1.)

Diagnostic Electroencephalography. By Hans Strauss, M.D., associate in neurology in charge of electroencephalography, Mount Sinai Hospital and Hospital for Joint Diseases, New York City; Mortimer Ostow, M.D., Med.Sc.D., adjunct in neurology in charge of electroencephalography, Beth Israel Hospital, and adjunct in neurology for electroencephalography, Mount Sinai Hospital, New York City; and Louis Greenstein, M.D., adjunct in neurology for electroencephalography, Mount Sinai Hospital, New York City. 4°, cloth, 282 pp., with 46 illustrations. New York: Grune and Stratton, 1952. $7.75.

Intracranial Aneurysms. By Wallace B. Hamby, M.D., professor of neurologic surgery, University of Buffalo School of Medicine and Dentistry and Buffalo General Hospital. 8°, cloth, 564 pp., with 193 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $14.25.

NOTICES

ANNOUNCEMENT

Dr. Harold G. Tobey announces the removal of his office to 274 Commonwealth Avenue, Boston.

SOCIETY MEETINGS AND CONFERENCES

MAY 25–31. First World Congress on Fertility and Sterility. Page 1001, issue of December 18.

MAY 28–31. American Therapeutic Society. Page 746, issue of April 23.

MAY 30 AND 31. Society for Investigative Dermatology, Inc. Page 570, issue of March 26.

JUNE 3. Associated Diplomates of the National Board of Medical Examiners. Page 874, issue of May 14.

JUNE 6. Newer Concepts of Liver Disease. Drs. Franz J. Ingelfinger and Charles S. Davidson. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge. 10:05 a.m.

JUNE 7–9. American College of Cardiology. Page 395, issue of February 26.

JUNE 10–13. American Proctologic Society. Page 746, issue of April 23.

(*Notices concluded on page xix*)